Comprehensive care in Systemic Sclerosis

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Proefschrift

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Anne-Marie Adriana Schouffoer

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Paul Klee (1879-1940) leed vanaf 1935 aan diffuse Systemische Sclerose en overleed aan de gevolgen hiervan. Zijn werk werd de laatste jaren van zijn leven sterk beïnvloed door zijn ziekte. Het schilderij ‘diep in het bos’ maakte hij een jaar voor zijn overlijden.
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Promotiecommissie:

Promotores: prof. dr. T.W.J. Huizinga
prof. dr. T.P.M. Vliet Vlieland

Overige leden: prof. dr. J.H. Bolk
prof. dr. J.M. van Laar (UMC Utrecht)
prof. dr. A.M. Stiggelbout

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CHAPTER 1

Introduction

Introduction part I:

General overview Systemic Sclerosis (SSc)

Diagnosis and classification

Systemic sclerosis (SSc; scleroderma) is a generalized disorder of the connective tissue with unknown etiology and highly variable expression. It is characterized by Raynaud's phenomenon, small vessel vasculopathy, inflammatory manifestations and fibrosis. Skin tautness is the most apparent manifestation (1). The variability in disease course is illustrated by different patterns of skin tautness as well as differences in organ system involvement. Based on clinical characteristics, SSc can be divided roughly into a) limited cutaneous SSc (LcSSc) with skin tautness of distal extremities and usually moderately and slowly evolving organ fibrosis; b) diffuse cutaneous SSc (DcSSc) with rapidly progressive fibrosis including proximal extremities and/or trunk and more severe organ damage. In order to document and quantify skin changes over time, several scoring systems have been proposed, of which the modified Rodnan Skin Score (mRSS) has been best studied and validated (2). The mRSS assesses skin thickness in 17 body surface areas using a 0 to 3 scale (figure 1).

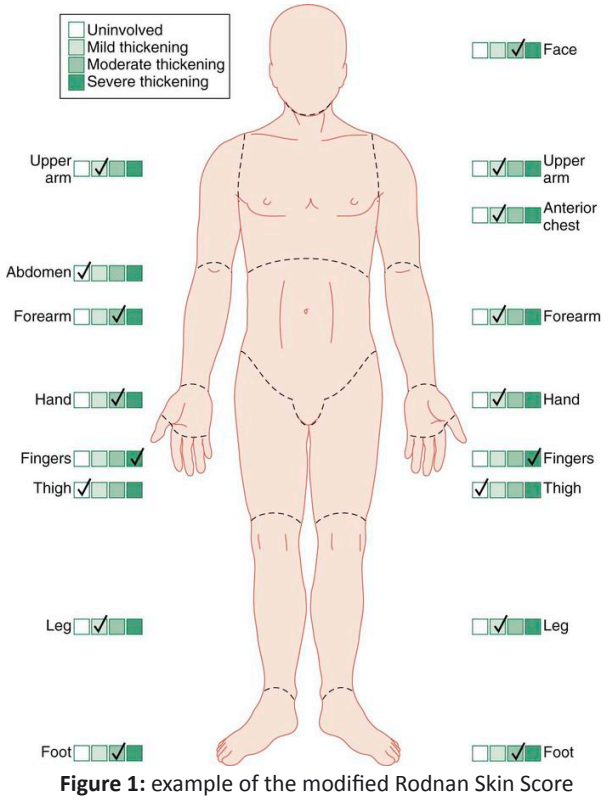

Figure 1: example of the modified Rodnan Skin Score

Microangiopathy is a predictor of the development of SSc and may precede other symptoms by many years (3). Nailfold videocapillaroscopy (NVC) is a non-invasive and safe diagnostic tool that illustrates microvascular damage. Moreover, in SSc different nailfold patterns can be defined; early pattern (few giant capillaries and hemorrhages without evident loss of capillary density); active pattern (frequent giant capillaries and hemorrhages and moderate loss of capillary density); and late pattern (ramified/bushy capillaries, few giant capillaries and hemorrhages, severe loss of capillary density) (4). A dynamic transition of microvascular damage through different NVC patterns of microangiopathy was demonstrated with clinical symptoms progressing in accordance with the nailfold morphologic changes in 60% of the SSc patients (5). Moreover, the different patterns correlate with auto-antibodies and clinical disease manifestations (6).

Preliminary criteria for the classification of definite Systemic Sclerosis of the American College of Rheumatology were established in 1980 (7). In daily practice however, these criteria demonstrated low sensitivity in early and limited SSc (8). Revised classification criteria were proposed by leRoy (9) including three subtypes; a) limited cutaneous SSc (lcSSc), b) diffuse cutaneous SSc (dcSSc) and c) limited non cutaneous SSc (lSSc) without skin involvement. People with either *objective* Raynaud's phenomenon, SSc-type nailfold capillary pattern *or* SSc selective autoantibodies, or *subjective* Raynaud's phenomenon, SSc-type nailfold capillary pattern *and* SSc selective autoantibodies are classified as having limited non cutaneous SSc. Other classification propositions based on prospective studies include diffuse (truncal), intermediate (extremities but not the trunk) and limited (fingers only) subtypes (10).
Recently, ACR/EULAR criteria for the classification of SSc were published (Table 1); according to this classification patients with a total score of ≥9 can be classified as having definite SSc (11). In a validation sample of 405 patients, these criteria resulted in a sensitivity of 0.91 (0.87–0.94) and specificity of 0.92 (0.86–0.96).

Auto-antibodies

SSc specific auto-antibodies may help to establish a diagnosis, but the absence does not exclude systemic sclerosis. Up to 11% of patients with SSc can test negative for antinuclear antibodies. An overview is listed in table 2 (12). The performance characteristics of anti-body testing in SSc depend on the clinical context in which they are used; for anti-Scl70 in SSc patients versus healthy controls an overall sensitivity of 0.20 and specificity of 1.0 was found and in SSc patients versus persons with primary Raynaud's phenomenon a sensitivity of 0.28 and specificity 0.98 was established (13). Anti-centromere antibodies demonstrated an overall sensitivity of 0.33 and specificity of 0.99 in SSc patients versus healthy controls.

Table 1. The American College of Rheumatology/European League Against Rheumatism criteria for Systemic Sclerosis (11)

Item	*Sub item*	**Weight**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)		9
Skin thickening of the fingers (only count the higher score)	Puffy fingers Sclerodactyly (proximal to PIP's)	2 4
Fingertip lesions (only count the higher score)	Pitting scars Digital tip ulcers	3 2
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)		2
Raynaud's phenomenon		3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III)		3

The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy)

Table 2. Auto-antibodies in scleroderma (12)

Anti-body	**ANA staining pattern**	**% in all patients**	**Clinical characteristics**	*Organ involvement*
Anti-Scl70*	speckled	10-40	dcSSc	lung fibrosis
Anti-Centromere		15-40	lcSSc	PH, esophageal disease
Anti-U1 RNP	speckled	5-35	lcSSc, black patients, polymyositis	muscle
Anti-RNA polymerase III	fine speckled nucleolar	4-25	dcSSc	renal, skin, PH
Anti-U3 RNP§	nucleolar	1-5	dcSSc, black patients, poor outcome	PH, muscle involvement
Anti-PM-Scl	nucleolar	3-6	overlap, mixed	muscle
Anti-Th/To	nucleolar	1-7	lcSSc	PH, lung fibrosis, small bowel
Anti-U11/U12	nucleolar	1-5	lcSSc and dcSSc	lung fibrosis
Anti-Ku		1-3	Overlap	muscle, joint,

* topoisomerase I; PH=pulmonary hypertension; § fibrillarin

Epidemiology

SSc is a relatively rare disease. The prevalence of SSc in the Netherlands, using the ACR preliminary classification criteria and leRoy's criteria, was estimated to be 8.9 per 100.000 inhabitants (14). This rate was based on the number of included patients in the POEMAS registry (Pulmonale hypertensie Opsporing Een multidisciplinaire Aanpak bij Sclerodermie), combined with a questionnaire sent to both academic and non-academic rheumatologists not participating in the POEMAS registry. Using the estimated prevalence rate of 8.9 per 100.000, the total number of patients living with SSc in the Netherlands is about 1500. The estimated prevalence is comparable with other North European countries, including Norway (9.9/100.000) (15) and 8.8/100 000 in northwest England (16). In southern European countries the estimated prevalence range from 15.8/100.000 in France (17) to 27.7/ 100.000 population in Spain (18), supporting a north-south SSc prevalence gradient. In the United States of America a prevalence of up to 24.2/100.000 was reported (19) in the Detroit area. Differences in prevalence among countries may also be explained by differences in ethnic background (20), the methodology used to identify patients with SSc (21), or inclusion criteria.

Prognosis

Mortality in SSc is high; in a systematic review and a meta-analysis of the literature (22) including 2691 SSc patients in 9 cohort studies, the pooled Standardized Mortality Ratio was (SMR) was 3.53. Among 732 deaths, heart involvement was the most frequent cause of death (29%), followed by lung involvement (22). In the EULAR Scleroderma Trials and Research group (Eustar) database (23), 55% of deaths were due to SSc, whereas 45% of deaths were thought to be unrelated to SSc. Of the SSc-related deaths, 26% were cardiac (predominantly heart failure and arrhythmias), whereas 29% of non-SSc related deaths were due to cardiac causes.

In the above mentioned systematic review (22) adjusted meta-regression analysis did not show significant change in SMR over time when comparing a 3 time cohorts (< 1980, 1980-90 and > 1990). In contrast, in a British cohort (24), five-year survival among diffuse cutaneous SSc (dcSSc) patients improved from 69% in a historical cohort (1990-1993) to 84% in a contemporary cohort (2000-2003), with dramatically more diagnoses of clinically significant Interstitial Lung Disease (ILD) and Pulmonary Arterial Hypertension (PAH). The 5-year survival among the limited cutaneous SSc (lcSSc) patients remained unchanged.

In a Canadian single centre study (25) including 158 patients seen between 1994 and 2004, the 5-year survival was 90% (95% for limited and 81% for diffuse) and the 10-year survival was 82% (92% for limited and 65% for diffuse). Deceased persons were more likely to have had dcSSc, cardiac disease, ILD, gastrointestinal disease, and systemic hypertension.

Disease manifestations

Myocardial disease

Cardiac involvement can be primary or secondary to Pulmonary Arterial Hypertension (PAH), Interstitial Lung Disease (ILD), or kidney disease. Cardiac abnormalities may include pericarditis, microvascular coronary artery disease (with resultant myocardial ischemia), conduction abnormalities (including bradyarrhythmias and tachyarrhythmias) and impaired myocardial contractility or relaxation with our without clinically overt heart failure (31).

Myocardial dysfunction seems mainly due to myocardial fibrosis, which might be the result of recurrent ischemia reperfusion injury due to microangiopathy, vasospasm and poor vasodilator reserve, and of inflammation (when present). Several studies demonstrated that diffuse cutaneous SSc, rapid progression of skin thickening, and older age at SSc onset are all risk factors for cardiac involvement in SSc (27-29). In a 7 year prospective study, severe cardiac Raynaud was found to be a strong long-term predictor of systolic LV dysfunction in SSc patients (30).

Myocardial fibrosis was seen in a post mortem study in 70% of patients with systemic sclerosis as compared to 37% in controls (31). More recently, myocardial fibrosis was demonstrated by delayed enhancement in 24/36 scleroderma patients undergoing MRI investigation (32). Conventional echocardiography assessment of left ventricular (LV) systolic function (based on measurement of the LV ejection fraction) has shown low sensitivity in demonstrating myocardial abnormalities, being able to identify only 5% of patients with cardiac involvement (27). The discrepancy between findings of myocardial fibrosis by histological investigation on the one side and clinical studies using conventional echocardiography methods on the other has led to a search for more sophisticated techniques for the assessment of LV function. One of these techniques, Tissue Doppler Imaging (TDI), assesses myocardial tissue velocities and is able to provide information on longitudinal function at the mitral valve annular level, which is often earlier impaired by myocardial fibrosis and might therefore represent a more sensitive parameter in identifying subtle cardiac dysfunction. Main measures by TDI are S', systolic myocardial velocity, E', early diastolic myocardial relaxation, and Aa, myocardial velocity associated with atrial contraction at the end of ventricular filling. In particular, S' at the lateral mitral annulus is a measure of longitudinal systolic function and is correlated with measurements of LV ejection fraction, while E' and A' are measure of myocardial relaxation. An example of the role of TDI in patients with SSc was demonstrated in 100 SSc patients with both limited and diffuse subtype disease. A trend towards a significant difference in LVEF was seen as compared to age- and sex-matched healthy controls; 64.9 (SD 0.6) versus 67.2 (SD 0.7) (p= 0.069) (33). Decreased contractility as determined by S' < 7.5 cm/second SSc was seen in 14

patients, as compared with none of the controls (P = 0.040), suggesting a relatively high prevalence of reduced LV contractility. However, myocardial analysis by TDI is significantly limited by angle dependency (the measure changes with the insonation angle) and does not allow the evaluation of all LV segments and of different directions of myocardial deformation. Recently, two-dimensional (2D) speckle tracking analysis has been proposed as a sensitive and accurate method for the evaluation of subclinical myocardial dysfunction, providing measures of LV regional and global strain in three orthogonal directions (longitudinal, circumferential and radial), overcoming the limitations of TDI (34).

Pulmonary disease

The major pulmonary complications of SSc are Interstitial Lung Disease (ILD) and Pulmonary Hypertension (PH) (35). ILD may lead to a restrictive lung function pattern and is difficult to reverse since curative therapies are not yet available. Early identification and appropriate monitoring of patients with SSc complicated by PAH and/or ILD is challenging but mandatory, so that active pulmonary disease may be controlled and tissue damage prevented or delayed. The most common pathological finding in lung biopsies of ILD in 80 patients with SSc was Non-Specific Interstitial Pneumonia (NSIP), although Usual Interstitial Pneumonitis (UIP) was also occasionally found (36). In this study including only patients of whom surgical lung biopsies was obtained, disease outcome was found to be linked more strongly to disease severity at presentation and serial DLCO trends than to histopathologic findings.

The prevalence of interstitial lung disease depends on the diagnostic tool that is studied. High Resolution Computed Tomography (HRCT) and pulmonary function testing, particularly Forced Vital Capacity (FVC) and Lung Diffusing Capacity for Carbon Monoxide (DLCO), are currently used to define and monitor lung fibrosis, respectively. There is a wide range in normal pulmonary function testing (FVC 80-120% predicted), depending on the lower limit of normal (LLN) (37), so in the disease course it is the degree of reduction from a premorbid level that may indicate development of lung disease. In Idiopathic Lung Fibrosis patients a DLCO threshold at baseline of 40% predicted and a decline during follow up of the Forced Vital Capacity > 10% and DLCO > 15% has been associated with increased mortality (38). Steen at all showed that a major decline in FVC occurs within the first 4–6 years of onset of systemic sclerosis, resulting into a moderate to severe restrictive lung disease in 40% of SSc patients (39). HRCT proves to be very sensitive for the detection of SSc-ILD. In a study quantifying the prognostic value of baseline pulmonary function testing and HRCT, 277/330 (84%) SSc patients had evidence of ILD (40). In another smaller series of 23 SSc patients, 91% showed ILD on HRCT, whereas only 31% of the same patients showed abnormalities on chest X-ray (41). Recently, based on predictors of mortality, Wells et all presented a simple algorithm with SSc-ILD staged as limited disease (minimal disease on HRCT or,

in indeterminate cases, FVC ≥70%) or extensive disease (severe disease on HRCT or, in indeterminate cases, FVC <70%) (40).

Estimates of the prevalence of pulmonary hypertension (PH) in patients with SSc range from 4.9% (17 of 344 patients) (42) to 38% (16 of 47 patients) (43), with an average rate in multiple studies of 16% (300 of 1.837 patients) (44). The widely ranging prevalence is due to the use of various definitions and diagnostic criteria and various measurement methods (with or without right hart catheterization (RHC). Pulmonary arterial (precapillary) hypertension is defined as a mean pulmonary artery pressure measured by RHC of >25 mmHg at rest and a pulmonary capillary wedge pressure (PCWP) < 15 mmHg. Raised N-terminal probrain natriuretic peptide (NTproBNP) levels are directly related to the severity of PAH and baseline and serial changes in NTproBNP levels are highly predictive of survival in SSc-PAH (45). PAH is a serious disease complication; in 131 SSc patients with incident PAH who were followed for a mean of 2.0±1.4 years. 1-, 2-, and 3-year cumulative survival was 93%, 88%, and 75% (46).

An average delay between symptom onset and the actual diagnosis of PAH of ≥ 2 year was demonstrated, which may be explained by initially non-specific symptoms such as fatigue or breathlessness and lack of fitness, as well as concurrent diagnoses such as heart failure or ILD (47).

In a retrospective study including 815 SSc patients who had a lung function performed, 19% had an isolated reduction in DLCO (48). This group of patients was younger, and, as can be expected, included more past or present smokers. Subsequently, a subset of 11% developed isolated pulmonary hypertension. In this group, pulmonary hypertension was strongly associated with an initial DLco of < 55% of predicted normal and a FVC (%predicted)/DLco (% predicted) ratio of >1.4. Patients with a poor outcome demonstrated an initial DLCO < 50% predicted. Isolated PAH is less common in diffuse scleroderma, and when present it is often seen with patients with the nucleolar antibody anti-U3-RNP (49).

Annual systematic screening resulted in more complete ascertainment of lung complications and substantial improved survival for the diffuse cutaneous subset of SSc patients (24). SSc PAH detection programs were able to identify patients with milder forms of the disease, as compared with patients in routine clinical practice, allowing earlier management (50). However, although early intervention by PAH-targeted treatment demonstrated benefits in mildly symptomatic (majority idiopathic) PAH patients (51), a clear benefit for early treatment in SSc-PAH has not yet been established. Current guidelines recommend annual echocardiography screening for symptomatic PAH patients, and state that annual screening may be considered in asymptomatic patients (52). For patients with SSc and SSc spectrum disorders expert opinion recommend echocardiography screening and a pulmonary function test annually and in case of new symptoms (including NT-ProBNP) (53). A detection algorithm “DETECT” that was recently proposed (54), includes 6 simple assessments (FVC % predicted/DLCO

% predicted, current/past telangiectasias, serum anti-Centromere antibody, serum NTproBNP, serum urate and right axis deviation on ECG), and defines a need for referral to echocardiography in case of a total risk points > 300 (Step 1). Two echocardiographic variables (Right Atrial area and tricuspid regurgitant jet (TR) velocity) and the total risk points from Step 1 were included in Step 2 in order to determine the need for referral for RHC. Of 466 SSc patients (with an increased risk of PAH) included in this study, 87 (19%) had RHC-confirmed PAH. The DETECT algorithm recommended RHC in 62% of patients (referral rate) and missed 4% of PAH patients (false negatives).

Renal disease

Renal involvement in SSc includes scleroderma renal crisis (SRC), normotensive renal crisis, antineutrophil cytoplasmic antibodies-associated glomerulonephritis, penicillamin-associated renal disease, and reduced renal functional reserves manifested by proteinuria, microalbuminuria, or isolated reduction in glomerular filtration rate (55). SSc renal crisis (SRC) is most often seen in patients with a disease duration less than 4 years, early or rapidly progressive diffuse skin involvement and presence of friction rubs. In European patients, a prevalence of 4.2% in patients with dcSSc and 1.1% in lcSSc was seen (35). Anti-RNA polymerase III antibodies are identified as the most important risk factor, with a 25% risk of developing SRC (independent of corticosteroid exposure), compared with a 2% risk in the absence of this antibody (56). Use of glucosteroids > 15 mg/day are another risk factor that was identified (57;58). The dramatically reduced mortality due to SRC in the past decades (59) may well be the result of prompt and adequate therapy. Administration of Angiotensin Converting Enzym (ACE) inhibitors as first line treatment with careful titration of blood pressure is recommended, with Angiotensin II receptor blockers (ARBs), calcium channel or *a* antagonists added if necessary (60). The preventive rol of ACE inhibitors in SRC is a subject of discussion. In a retrospective study 23/91 (25.3%) SRC patients used ACE inhibition at SRC onset versus 82/427 (19.2%) SSc controls (57).

Gastro intestinal disease

The prevalence of gastrointestinal involvement depends on the diagnostic tool that is used for evaluation. In an autopsy study, GI muscle atrophy and/or fibrosis was found in the esophagus, small intestine, and large intestine in 74%, 48%, and 39% of patients, respectively (61). Myopathic changes in the intestine are thought to be preceded by a neuropathic phase (62). SSc involvement of the GI tract affects motility, digestion, absorption and excretion. Symptoms in both limited as diffuse SSc patients include pain, dysphagia, reflux, early satiety, bloating, emesis, diarrhoea, constipation, faecal incontinence and substantial weight loss. Bleeding from telangiectasias and gastric antral vascular ectasia (GAVE, or watermelon stomach) is more often seen in elderly patients with limited SSc (63). Malabsorption may also be due to pancreatic insufficiency or bacterial overgrowth.

Muscular, osteo-articular, skin and soft tissue involvement

In the early disease course the skin may be swollen with a shiny appearance (64). The fingers may have a 'puffy' aspect and patients may complain of pain or itch. A loss of strength of the hands, sometimes combined with a feeling of numbness in the fingers, is often interpreted as a carpal tunnel syndrome. In active disease, fibrinous deposits in tendon sheats may result in a rubbing sound when a joint is moved, so called tendon friction rubs. As fibrosis advances, microstomia may develop as well as flexion contractures in hands and in diffuse SSc more proximal sites. Joints may be stiff and painful due to arthritis and/or tendinitis , myositis can be present with often moderately elevated creatine phosphokinase (CPK) (65). Musculoskeletal manifestations were almost twice as common in dcSSc as in lcSSc in 3656 patients included in the EUSTAR database (35).

Sicca syndrome is common in SSc, almost always due to salivary fibrosis (66). Patients with SSc and associated Sjögren's syndrome are more likely to have other auto-immune disorder or other autoantibodies and demonstrate a lower frequency of lung fibrosis then SSc alone. Soft tissue and vascular involvement of the urogenital system may result in physical and psychological complaints in both female and male SSc patients (67;68).

Psychological functioning

Patients with SSc have to cope with an uncertain disease course, variable impact on physical functioning and limited therapeutic options. Moreover, patients are often confronted with altered appearance due to scleroderma facial features, skin sclerosis, contractures, teleangiectasias, pigment changes and digital ulcers. In recent years, growing awareness is seen for the psychological distress that is associated with the disease. A systematic review of the literature found that apart from reduced physical quality of life, mental quality of life was significantly impaired in SSc patients (69).

In a review by Thombs (70), a prevalence of mild-to-moderate symptoms of depression was found in 51%-65% of SSc patients fulfilling ACR criteria. Evaluation with a more conservative cut-off score identified 46% and 56% of patients. In a cross-sectional study, 18 % of 376 SSc patients demonstrated scores indicating probable depression, with sociodemographic and individual disease severity indicators (tender joint count, number of gastrointestinal symptoms, and breathing difficulties) significantly related to symptoms of depression (71). Matsuura et al found depressive symptoms were ranging from mild to severe state in 46% of 50 patients, with measures of depression being significantly correlated with low working ability, low social activity, low Sense of Coherence (SOC), pain, and helplessness, and not associated with disease severity variables including skin score and internal organ involvement (72). Moreover, multiple regression analysis showed that a high level of helplessness and a low level of sense of coherence might be closely associated with depressive symptoms in SSc. The authors

conclude that patients with a high level of helplessness or a low level of sense of coherence may be vulnerable to depression, and psychological interventions including counseling with special psychotherapists or antidepressant medication may prevent the development of depression.
In particular women with SSc were found to have lower self-esteem, than for example burns patients (73). Patients who were objectively rated as having more severe visible signs, had higher distress and felt more isolated (74). Van Lankveld et al found decreased appearance self esteem (ASE) in 123 SSc with low values in both diffuse and limited SSc (75). Female patients had lower ASE than male patients and higher levels of limitations were related to lower levels of ASE; the Health Assessment Questionnaire Disability Index (HAQ-DI) and subscales together explained 28% of the appearance self esteem questionnaire variance. Moreover, lower ASE was correlated with self-assessed disease severity as well as disease symtoms such as pain, Raynaud and tiredness. In contrast, physician assessed disease variables such as the Modified Rodnan Skin Score (2) were unrelated to ASE.

Outcome measurements

In the clinical assessment of patient, both self reported measures as well as physical examination and organ specific tests are useful in monitoring disease course and treatment effect. Moreover, properly validated measures are essential in observational studies and clinical trials. Many disease measures in Systemic Sclerosis have been described, the essentials are summarized below and references if possible are added.

General:

Inflammatory markers, anemia, auto-antibodies,

Aerobic capacity

Exercise testing (ergometry), exercise oxygen saturation, oxygen uptake (VO_2), production of carbon dioxide (VCO_2), ventilation (VE), six minute walk distance (6MWD), functional class (New York Heart Association)

Cardiac function:

Electrocardiogram, echocardiography, heart catheterization, CT (angiography), MRI, cardiac scintigraphy (ejection fraction),

Pulmonary function

VAS dyspnoe, blood gas analyses, pulmonary function tests particularly forced vital capacity (FVC) (measured by spirometry) and diffusion lung capacity of carbon monoxide (DLCO single-breath), bodybox (Total Lung Capacity), imaging (High Resolution CT scan), ventilation/perfusion (V/Q) lung scan. Saint George's Respiratory Questionnaire (76),

Gastro-intestinal function

upper GI endoscopy, pH studies, oesophageal manometry, electrogastrographic recording, gastric scintigraphic evaluation, faeces sampling/cultures, hydrogen breath test, endosonography. University of California, Los Angeles Scleroderma clinical trials consortium gastrointestinal scale (UCLA SCTC GIT) 2.0 (77)

Renal function:

Urinalysis, creatinin and glomerular filtration rate (GFR), proteinuria, renal biopsy, renal vascular resistive index (78).

Muscular, osteo-articular, skin and soft tissue involvement

modified Rodnan Skin score (2), skin durometer, maximal mouth opening, Mouth Handicap In Systemic Sclerosis questionnaire (79), Cochin Hand Function Scale (80), Hand Mobility In Systemic Sclerosis (HAMIS), Michigan hand questionnaire, Hand Anatomic Index, Kapandji hand index, Fingertip Palm Distance, grip strength, pinch grip, digital ulcer burden,

Sexual function

Sexual Relationships subscale of the PAIS-SR, Female Sexual Function Index, Female Sexual Distress Scale

Raynaud's phenomenon (RP) (81)

Raynaud Condition score, RP attack frequency (no. per day), RP attack duration (minutes), HAQ VAS for RP, Physician's assessment of RP (by VAS), Patient's assessment of RP (by VAS)

Digital ulcer (81)

SHAQ VAS for digital ulcers, Physician's assessment of digital ulcers (by VAS), patient's assessment of digital ulcers (by VAS)

Daily activities and Body functions:

HAQ DI and SHAQ (82), UK Scleroderma Functional Score (UKFS) (83), Scleroderma Assessment Questionnaire

Mental / psychological functions:

Beck depression inventory, Center for Epidemiological Studies Depression Scale (CES-D), Hospital Anxiety and Depression Scale (HADS-D), Delusions Symptoms States Inventory/states of Anxiety and Depression scale (DSSI/sAD), Montgomery-Asberg Depression Rating Scale (MADRS), Fear of Progression Questionnaire-Short Form (84), Satisfaction with Appearance Scale (85),

Illness Cognition Questionnaire, Illness Perception Questionnaire, Psychosocial Adjustment to Illness Scale (PAIS-SR) (86)
Adapted Satisfaction with Appearance (SWAP) scale (85)

Quality of life

Short Form SF-36, EuroQol 5 D, Symptom burden index (87), Cambridge Pulmonary Hypertension Outcome Review (McKenna 2006)

Environmental factors

Evaluation of Daily Activity Questionnaire (EDAQ) (88)

Pharmacological treatment of Scleroderma

Treatment options in SSc consist of supportive medication on one hand and therapy that aims to reduce inflammation, fibrosis and vasculopathy on the other. Examples of supportive measures are antibiotic therapy, indicated for infectious complications (digital ulcers, interstitial lung disease with bronchial hyper reactivity or bronchiectasias), local therapy, wound dressing and consultation by plastic surgeon in case of complicated calcinosis cutis or digital ischemia and dietary measures needed in case of malnutrition. So far a cure is not available. The vascular, inflammatory and fibrotic processes in SSc have a variable expression and often unpredictable disease course. In the past years, treatment targeting involved organs has been the hallmark of SSc management. Early recognition of complications is therefore crucial. Therapy must be tailored to the individual patient depending on the extent and severity of organ involvement and the patho-physiologic stage of the disease; active or inactive. A number of targeted treatments are listed in table 3. Most of them have been assessed in a randomized controlled trial (RCT) or have been recommended by expert opinion (89).
A few novel immune modulatory therapies demonstrated promising results in recent years; Mycophenolate Mofetil (MMF) (90), Rituximab (91;92), and autologous haematopoietic stem cell transplantation (93). Anti-fibrotic treatment by Imatinib was found to have variable effectiveness and poor tolerability in SSc trials (89).

Tabel 3. Pharmacological treatment overview

Clinical feature	Treatment options
Raynaud's phenomenon	Calcium channel blockers, alpha-blockers, serotonin inhibitors, angiotensin II receptor inhibitors, local nitrates, iloprost
Digital ulcers healing	Iloprost, phosphodiestherase inhibitors
New digital ulcers prevention	Bosentan
Calcinosis cutis	Calcium channel blockers, colchicine, minocycline
Scleroderma	Methotrexate
Interstitial Lung Disease	Cyclophosphamide (with/without corticosteroids), azathioprine
Pulmonary arterial hypertension	Endothelin receptors antagonists, phosphodiestherase inhibitors, prostanoids
Esophageal reflux	Proton pump inhibitors, pro-kinetics
Intestinal bacterial overgrowth	Broad spectrum antibiotics
Arthritis	Corticosteroids, methotrexate
Myositis	Corticosteroids, azathioprine, methotrexate, immunoglobulins
Serositis (pericarditis, pleuritis)	Corticosteroids, cyclophosphamide
Scleroderma renal crisis	Angiotensin converting enzymes inhibitors, angiotensin II receptors inhibitors, calcium channel blockers

Non-pharmacological treatment of Scleroderma

The combination of impaired physical as well as mental quality of life and limited therapeutic options warrants appropriate guidance by health professionals and the provision of non-pharmacological treatment. This may focus on limitations in physical functioning or psychosocial functioning or both.

Physical rehabilitation

Studies evaluating the effectiveness of non-pharmacological care in SSc have a large variety in interventions as well as outcome measures. Moreover, research on this subject is hampered by small sample sizes and a low methodological quality of studies. In a review on musculoskeletal rehabilitation in SSc, a number of studies were described evaluating modalities as paraffin waxing, range of motion exercises, splinting, massage and general exercise (94). These techniques were either applied alone or in combination, which makes comparisons complicated. An overview of the most relevant rehabilitation studies in SSc is presented in Appendix 1. With the limitation of the available literature taken into account, a few assumptions can be made:

- range of motion exercises and connective tissue massage with joint manipulation of the hands may improve joint motion

- prior paraffin treatment may support stretch exercises
- range of motion and stretching exercises can be effective in increasing mouth opening
- splinting has not proven to be effective for flexion contractures
- there is limited evidence for increased muscle strength, improved quality of life and reduced disability after general exercise programs with partly sustained results. An increased peak oxygen uptake was seen in a selected group op SSc patients without interstitial lung disease, without information on post treatment sustainment.

Psychological support

The awareness for the need for psychological support is growing in recent years resulting in a number of publications. A few educational programs were described (95;96), including self-management programs. Only recently, two more specific psycho-educational programs, including cognitive behavioural modules were published. Kwakkenbos et al demonstrated statistically significant, yet small improvements of helplessness and acceptance in patients who participated in a program consisting of 7 psycho-educational sessions of three hours in 5 weeks. Other studies did not include measures of effectiveness. An overview of the literature is presented in Appendix 2.

Introduction part II:

Health status in SSc according to the International Classification of Functioning, Disability and Health (ICF)

The International Classification of Functioning, Disability and Health (ICF) of the World Health Organisation WHO is a useful framework for describing and understanding the impact of SSc on the patient (97). From a medical point of view, the consequence or outcome of a disease is usually expressed as physical (dys)function or (dis)ability (morbidity). The WHO initiated the development of ICF classifications for established diseases, and placed the patient's perspective in the center of this framework instead of his/her condition. Thus, functioning according to the ICF classification also includes patients' activities and participation in society. Moreover, the influence of environmental factors, patients' personal characteristics and interaction with the environment on (dys) function are taken into account in the ICF model (98). If a person with a given health condition lives in an environment characterized by barriers at every level their performance will be restricted; but if a person lives in a facilitating environment this will serve to increase their performance.

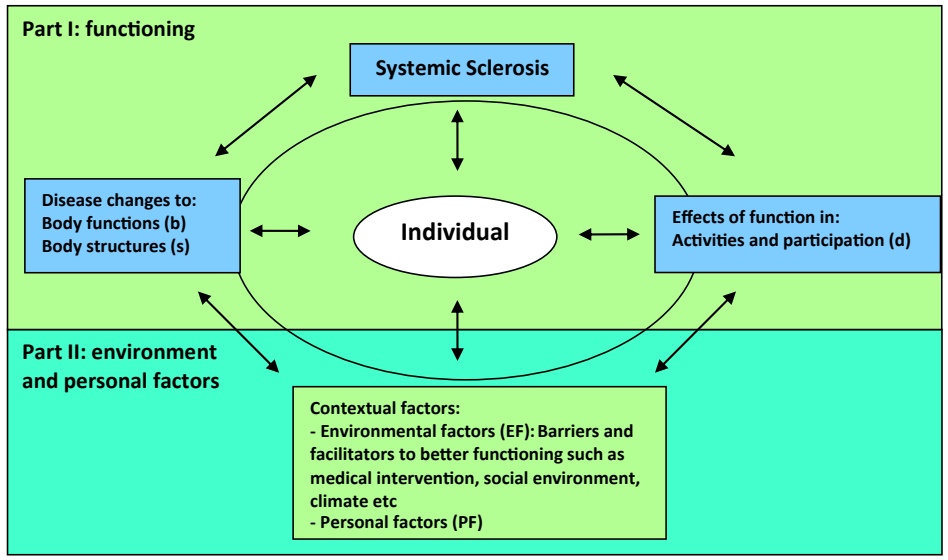

Figure 2: Health status in SSc according to the International Classification of Functioning, Disability and Health (ICF)

The first part of the ICF classification describes the type and degree of various functioning impairments, limitations and restrictions related to or associated with a condition. There are 1454 classifications rubricated in a detailed structure, enabling comparisons between patients, diseases or nations in “ICF language”. In the clinical context, the ICF can be used for the assessment of needs, matching interventions to specific health states, rehabilitation and outcome evaluation.

Body function (b) levels include: b1 mental functions, b2 sensory function and pain, b3 voice and speech functions, b4 functions of cardiovascular, hematological, immunological and respiratory system, b5 functions of the digestive, metabolic and endocrine system etc. These can be specified into a second and third level. In practice: b5 concerns the first-level of classification ‘Functions of the digestive, metabolic and endocrine systems’; b510 concerns the second-level classification ‘Ingestion functions’; b5105 concerns the third level Swallowing and b51052 pertains to the more detailed classification of ’Esophageal swallowing’ (100). Severe impairment of esophageal swallowing can be described as b51052.4, where ‘4’ refers to a scale of 0-4 from 0 (no impairment) to 4 (complete impairment). If a code is not applicable, the code will be followed by ‘.9’.
Body functions (b), body structures (s), and activities and participation (d) belong to the part ‘functioning and disability’. Environmental factors and personal factors belong to the part ‘contextual factors’. Personal factors (p) (race, gender, age, educational level, coping styles, etc.) have not been classified because of the wide variability among cultures. The chapters for body structure (s) and body function (b) are parallel to each other for ease of use.

For clinical use or research a so called ICF core set can be developed, pertaining to a selection of ICF domains or categories from the whole classification which can serve as minimal standards for the reporting of functioning and health in patients with a certain illness. For rheumatoid arthritis a Delphi exercise resulted in a brief core set compromising 39 second-level categories (8 on body functions, 7 on body structures, 14 on activities and participation, and 10 on environmental factors) (99). For SSc, a core set is currently being generated (100). A core set is not intended to replace validated instruments, but may be helpful in clarifying to what extent these instruments describe disease experience.
Aspects of functioning and disability addressed in this thesis are body structures, body functions (physiological and psychological functions) and activities and participation.

A. Disease consequences in terms of body structures and functions

The inflammation, fibrosis and vasculopathy in the skin and internal organs leads to a variable degree of morbidity. The disease manifestation due to involved organ systems have been discussed in part I with body structures and function discussed together.

B. Disease consequences in terms of daily activities and societal participation

Daily activities
Limitation in daily functioning is common in SSc patients and may be due to skin fibrosis, sicca syndrome, musculoskeletal pain or impairment, vascular injury, gastro-intestinal symptoms, decrease in aerobic capacity and tiredness (101). Impaired aerobic capacity may be due to cardiac as well as pulmonary involvement and may lead to a decreased (submaximal) exercise performance (102), which is often used as a parameter to disease severity.
Significant disability in activities of daily living as expressed by the HAQ was demonstrated in patients with both the diffuse and limited subtypes of SSc (103), with the highest disability in the components activity and grip, and lowest in walking. Among the physical factors that were evaluated, extensive skin thickening and severe joint and muscle involvement had the highest correlation with global disability. Other studies confirmed that hand functional disability is the major component of global disability in patients with SSc (80). Limitations in daily activities were also evaluated using the Evaluation of Daily Activity Questionnaire (EDAQ) in thirty patients with SSc (88). This questionnaire includes 102 daily activities in 11 dimensions: eating/drinking, transfer, toileting, dressing, bathing, cooking, mobility indoors, cleaning, washing/clothes care, mobility outdoors/ shopping, and communication. Most limitations were seen in the dimensions Eating/Drinking and Washing/Clothes, and the fewest in Mobility indoors and Transfers.

Societal participation
The majority of patients with both diffuse as limited SSc perceive major consequences for their lives due to their illness (104). Disease symptoms of SSc may not only influence everyday self care and household occupations but also professional activity and hobbies (105;106). Work disability is usually defined as work cessation due to the disease prior to the age of retirement (107). Other definitions and endpoints that are employed in studies on the impact of SSc on work ability include absenteeism or sick leave, reduction in productivity while present at work (presenteeism) and productivity loss. The influence of SSc on work status is best determined by comparing clearly defined endpoints between SSc patients and matched controls living in the same area, taking differences in age, sex and other socio-demographic variables such as education into

account. This methodology was employed by Mau et al in Germany, who demonstrated reduced participation in labor force as expressed by standardized employment ratios in individuals with SSc (108). A number of recent studies found that lower educational level, less social support, poor functional ability and longer disease duration were associated with work disability (109;110).

C. Personal and external factors; health care usage and needs

Given the complexity of the disease, SSc patients usually require multidisciplinary treatment, involving the general practitioner, a rheumatologist, other medical specialists and non-medical health professionals such as physical therapists, occupational therapists, dieticians, nurses or psychologists. In a few available studies on health care utilization, the number of visits to the rheumatologist varied from 2.4 to 4.0 visits per year (111-113) and to the general practitioner from 3.5 to 10.3 visits per year. Only one of these studies focused on factors associated with health care utilization; higher skin scores, more co morbidity and worse physical functioning were associated with higher health care utilization (111). In a survey including 1437 members of 12 provincial chapters of the Scleroderma Society of Canada, 43 percent of SSc patients were diagnosed by a rheumatologist (114). Among patients with diffuse disease, 90% were followed by a rheumatologist; however just over half of patients had seen a gastroenterologist (54%), cardiologist (51%), pulmonologist (67%), and less than half had seen a dermatologist (42%), nephrologist (13%), physiotherapist (46%), or occupational therapist (34%).

A number of studies have investigated the unmet needs and preferences regarding health care delivery among patients with SSc, concluding that unmet health care and information needs are common (115;116). Rubenzik found health care needs in the psychological/spiritual/existential domain in a group of 25 patients with SSc (115). In addition, in a Dutch study in 123 patients with SSc, the need for practical information on disease background, medication usage and dealing with pain was identified (116).

Introduction part III:

Aims of this thesis

Due to the complexity of the disease, health care providers involved with Systemic Sclerosis patients experience challenges in diagnosis as well as monitoring of disease course and complications. As was demonstrated in the introduction, patients may have a large variability in symptoms, but in most patients substantial morbidity is present.
For good clinical practice minimal standards for the reporting of functioning and health in patients with Systemic Sclerosis are essential. For this purpose, a framework as the International Classification of Functioning, Disability and Health (ICF) may be helpful.

For this thesis, a general aim was to gain more insight into the impact of SSc on a number of aspects of patients' health , related to the ICF chapters Body functions and structures, Activities and participation and Contextual factors such as rehabilitation. The studies also examined the clinical and scientific value of a number of relevant disease outcome measures.

In Chapter 2 two-dimensional (2D) speckle tracking analysis was used to evaluated subclinical myocardial dysfunction, providing measures of LV regional and global strain in three orthogonal directions (longitudinal, circumferential and radial) and thus overcoming the limitations of TDI (34). Also the relationship of this technique with functional capacity and ventricular arrhythmias was investigated.

In Chapter 3 sexual functioning and distress of women with SSc was compared with healthy controls, and the association between sexual function and disease characteristics was evaluated.

In Chapter 4 French-generic Mouth Handicap in Systemic Sclerosis (MHISS) was translated, field-tested, adapted into Dutch language and its validity was tested. Complaints of mouth-opening restriction, dryness and esthetic concerns of patients with SSc can be monitored by this questionnaire.

In Chapter 5 the validity and responsiveness of the Michigan Hand Questionnaire (MHQ) in patients with SSc was assessed, a self-reported questionnaire with scores for overall hand function as well as ability to complete activities of daily living, pain, work performance, aesthetics and patient satisfaction. The MHISS addresses domains in hand functioning that are lacking in other questionnaires.

Since work is an important part of patient' participation, a systematic review was performed in Chapter 6 to evaluated work status and factors associated with work disability (WD) in patients with SSc.

In Chapter 7 a survey was done to establish how available health care services relate to healthcare needs of patients with SSc. Also, the association between needs and patient characteristics was studied and patients preferences regarding the provision of care was recorded.

Finally in Chapter 8 a randomized controlled trial evaluated safety and effectiveness of a multidisciplinary team care program provided by the Rheumatology Ambulatory department of the Leiden University Medical Centre by comparison with regular out patient care.

Appendix 1 rehabilitation studies in SSc

Author/ Design	Number	Method	Result
		Parrafin treatment	
Askew et al (117)	NRCT*, N=17, intervention (n=10) (5 own control), control (n=7). Disease duration not reported	Single paraffin bath 20 min, friction massage and active ROM. control no treatment. Pre and post measurement.	Unpaired paired samples significant improvement in skin compliance and overall functional, motion and strength. Paired samples not in motion and strength
Pils et al. RCT	RCT♦ , N= 16, intervention (n=8) and controls (n=8). Disease duration not reported	12 sessions of waxing after that, continued treatment or not. Measurement after 3 months.	No significant difference between the two groups
Sandqvist et al (118)	NRCT, N=17 control other hand Median disease duration 6 years	One hand once daily paraffin bath followed by finger flex/ ext, finger and thumb abduction, other hand once daily only exercise. Measurement after 1 month.	Intervention: significant larger improvements in finger ROM, perceived stiffness and skin elasticity. Controls: significant improved ROM finger flexion and extension in lesser extend.
Manusco & Poole (119)	Case studies, N=3, Mean disease duration 20 years	Paraffin and active hand exercises daily 8 weeks, measurements 0, 1 and 2 months.	Improvements in body function/ structure measurements, 1 of 3 in activity/participation
		Other hand function improvement	
Mugii et al (120)	NCT, N=42, 32 diffuse, 13 limited.mean, disease duration 5.0 years . Patients with arthritis and severe digital ulcers excluded	Each individual finger self administered stretching 3-10 x 10 sec/ day during 1 year. Total aprox 17 min/day. Conformation if the exercises were done correctly each month. Measurement 0, 1 and 12 months.	Significantly improved total passive joint motion in all fingers at 1 mnth and improved or maintained at 1 year. No change in total HAQ, but individual item scores eating and gripping significantly improved. Diffuse patients more improvement.

Maddali Bongi et al (121)	RCT , N=20, Intervention n=10, control n=10, disease duration 9.0 (SD4.1) years	Connective tissue massage and Mc Mennell joint manipulation (2x60 min/week) during 9 weeks. In case of edematous hands manual lymphatic drainage 2x60 min/ week. Controls only educational advices and medical information. Measurements at 0, 9 and 18 weeks.	Intervention: significant improvement HAMIS, CHFS, fist closure, mental and physical QoL, improved HAQ. Hand opening not improved. Improvement lost at 1 week follow up, except HAMIS. Control: no change. No comparison between groups.
Maddali Bongi et al (122)	RCT, N=40, Intervention n=20, control n=20, disease duration 8.7 (3.5)	Intervention 9 weeks program including facial, global and hand rehabilitation. Hand program: connective tissue massage 10 min per limb, Mc Mennell joint manipulation 15 min each side, and daily home exercise 20 min/day active finger movements and pinch. Total 2x25min/week and 20min/day during 9 weeks.. Control group daily home exercise. Measurement 0, 9 and 18 weeks.	Intervention: significant and partly sustained improvement of HAMIS, CHFS, Mental and physical QoL, HAQ and fist closure. Control: significant improved fist closure, not maintained at follow-up. No comparison between groups.
Seeger (123)	NRCT, N= 19, (8 completed) Median disease duration 2 years.	Intervention: Splinting 8 hr/day wrist, MCP, PIP Control: unsplinted hand	ROM not changed in intervention and control
Antonioli et al (124)	Intervention n=16, age 65,5, 4 diffuse, 12 limited SSc, disease duration 14.5 year (11-22) Control n=17, mean age 57, mean disease duration 9 (5-13) year	Intervention: general exercise program, including finger stretching, no details available. Total 10 x 30min day; warm-up, tredmill, walking, finger stretching, occupational therapy, additional therapy if needed. After 10 days home exercise during 4 mths. Controls: those who refused intervention participation. Measurement 2 and 4 months.	Intervention: significant improvement at 2 and 4 mnth of HAMIS, Control: no change.
Maddali Bongi et al (125)	NRCT , N=35. Intervention n=20, control n=20. Disease duration 8.0 (3,9) years.	Intervention: manual lymph drainage 1 hr/week, 5 weeks, Control regular care. Measurement at 0, 5 and 9 weeks.	At 5 week significant improved hand volume, HAMIS test, VAS edema, VAS edema and daily activity, VAS pain and daily activity, HAQ, SF-36 mental and physical component, as compared to control. At 9 week all but HAQ and SF-36 maintained.

		Oral therapy	
Naylor et al (126)	RCT, N=9, Intervention n=5, control n=4 Disease duration not reported	Intervention: active stretching 3x5/day, augmentation 2x/day. Control six “facial grimasing” 3x5/day. 3 mnth duration	Improvement maximal mouth opening (MMO) 5.6 mm intervention and 3.0 mm for control group; NS
Pizzo et al (127)	NCT, N=10 pts with MO <30 mm Disease duration not reported	Mouth-stretching 15 min 2x/day and oral augmentation exercises 1x/day, 18 week duration and measurement	MMO Baseline 26 (SD 1.76). Mean change 10.7±2.06, P < 0.0049.
Poole et al (128)	NCT, N=17, Diffuse (n=9); mean disease duration 10.5 years. Limited (n=8); mean disease duration 11.0 years	6 mnth intervention home program: education on oral hygiene, facial grimasing 3x5 stretches, each held for 3–5 sec and hand/mouth stretch 3x5/day held for 3–5 sec twice daily. Total aproximately 4 min/day.	MMO Baseline 49.1+7.5, No change in upper extremity measures or oral aperture. Improved oral hygiene baseline to 6 mnths.
Yuen et al (129)	RCT 4;3 block size, N=46 MMO <40 mm. Intervention (n=26), control n=22. Mean disease duration 7.6 years	Home exercise 3 times stretching exercises (held 15-20 seconds, 10 sec rest twice daily (total aprox 6 min a day) during 6 mnths with daily calendar monitoring. Controle usual dental care control. Evaluation 3 and 6 months	Intervention: non significant improvement of MMO baseline 36.5 ± 9.7 mm, 3 mnths +2.81 mm, 6 mnths +2.75 mm as compared to baseline. As compared to control significant improvement at 3 mnths. Controls no improvement.
Maddali Bongi (130)	RCT, N=40, Intervention n=20, control n=20, disease duration 9.4 (4.3) years.	Intervention 9 weeks program of connectivue tissue massage+ Kabbat’s method (focus on orbicularis oris,zygomaticus, levator labii and nasalis muscles+ kinesi therapy (total aprox 2x40 min/week) AND mouth-stretching (3x5 min /day, oral augmentation exercises 1-2x8/day and mimic exercises 1x/day (total aprox 35 min). Control : home exercise alone. Evaluation at 9 and 18 weeks.	Intervention: MMO at baseline 38.0 (SD 10.6.) 9 week 42.8 (9.9), 18 week 45.8 (11.6). Skin score (9 and 18 week) and MHISS (9 week) significantly improved. Control no improvement. No comparison between groups.

Maddali Bongi (121)	RCT , N=20, Intervention n=10, control n=10, disease duration 9.0 (SD4.1) years.	Intervention 9 weeks program including facial, global and hand rehabilitation. Facial program: connective tissue massage + Kabat's method, + kinesitherapy (2x60 min/ week). Controls only educational advices and medical information. Measurements at 9 and 18 weeks.	Intervention: MMO baseline 3.4 (SD 1.1), 9 week 4.0 (SD 1.2) p<0.05, 1 week 4.8 (SD 1.4) p <0.01. Controls no improvement. No comparison between groups. Intervention : Face-VAS baseline 3.7 (SD 1.3), 9 week 3.1 (SD 1.1) p <0.002, 18 week 3.8 (SD 0.9) NS. Controls no improvement. No comparison between groups
		General exercise	
Pinto et al (131)	NCT, N=11, Age 44 (13) year 3 diffuse, 11 limited SSc, disease duration 7.4 (1.8) years. Patients with pulmonary involvement excluded	12 week program 2 sessions/week Warming up, 30 min resistance training bench press, leg press, lat pull down, leg extension, and seated row, 20 min aerobic exercise, 5 min stretching. Measurement 0 and 12 weeks.	Significant improvement of muscle strength (leg press), significant reduced hart rate at rest, significant improvement of work load and time. No change in aerobic capacity.
Antonioli et al (124)	NRCT, N=33 Intervention n=16, age 65,5, 4 diffuse, 12 limited SSc, disease duration 14.5 year (11-22) Control n=17, mean age 57, mean disease duration 9 (5-13) years	Intervention: 10 sessions 30 min/ day; warm-up, tredmill, walking, finger stretching, occ therapy, additional therapy if needed. After 10 days home exercise Controls: those who refused intervention participation, regular care. Measurement 2 and 4 months.	Sign improvement at 2 and 4 mnth of physical and mental QoL, hand function (HAMIS), respiratory symptoms, decreased hart rate at exercise at 4 mnth. No change in HAQ, 6MWD,
Oliveira et al (132)	NRCT, N=14 Intervention n=7, age 45.57 ± 8.22, 2 diffuse, 5 limited, disease duration 12.6 ± 7 years. Rodnan skin score 15.8 (7.8). Control n=7 healthy subjects.	8 week program, aerobic exercise 40 minutes/ 2x/week Measurement 0 and 8 weeks	Both groups significant peak VO2 max, no significant difference between groups. In SSc group higher excise intensity (lactate) and improved peak oxygen saturation. No difference in QoL,
Maddali Bongi et al (121)	RCT , N=20, Intervention n=10, control n=10, disease duration 9.0 (SD4.1) years .	Tailored program: hand, face and global treatment 9 week. Global rehabilitation: hydrokinesy therapy 1 hr/ week or land based exercises 1 hr/week (stretching, pulmonary exercise, muscle strengthening, mobility, balance) Controls only educational advices and medical information. Measurements at 9 and 18 weeks.	Intervention: significant improved mental and physical QoL, improved HAQ, not maintained at 18 weeks. Controls no improvement. No comparison between groups

Appendix 2: psychological support studies in SSc

study	*characteristics*	*Intervention*	*measures*	*results*
Samualson (95)	Case study, N=6, mean age 62 (47-74), disease duration 8 (4-11)	Educational program 7 sessions 3 hr /5 weeks Living with scleroderma, medical aspects, anatomy, home training program, leisure time and exercise, pain and pain control, diagnosis and treatment, occupational therapy, psychological aspects, benefits of physical therapy, hand function, and thermotherapy and hand exercise, joint protection, activity daily living, skin care, dietary matters, ergonomics, scleroderma influence on social participation.	HAQ, arthritis self-efficacy scale, psychological general well-being index, VAS pain and global health.	Global evaluation indicating patients satisfaction.
Genth (96)	Pilot	Educational program 7 sessions 3 hr /5 weeks, groups 6-12 persons. Diagnosis and treatment, physical therapy, occupational therapy, coping with disease and stress, personal hygiene and cosmetics, sexuality and relations,	No measurements published	No results published

Buenaver *(133)*	N=3, case study	Cognitive-Behavioural treatment by minimal contact manual for scleroderma. Two in-person sessions and five telephone sessions with a psychologist. Written material with eight chapters presented as eight weekly sessions. 1. Introduction and relaxation training 2 Answering people's questions about scleroderma; goal setting 3 Having fun, pacing, and using rewards 4 Cognitive therapy—understanding how negative thinking impacts mood 5 Developing balanced thinking and disputing negative thoughts 6 Pain, fatigue management, and coping skills 7 ABCDs of body image dissatisfaction 8 Communication skills, active listening, and assertiveness	Global evaluation	One patient with successful new pacing routine and reduction of pain and fatigue, one patient with global benefit but needing more time than initially planned, one patient without benefit due to education-related obstacles
Kwakkenbos (134)	NCT N=41, diffuse 37%, limited 63% mean age 52.8 (12.2)	Psycho Educational Group program, 6-10 patients 13 modules 1.5 hr/three weekends Goal setting, disease characteristics, diagnosis and treatment, occupational therapy, psychological aspects, benefits of physical therapy, Measurement -6 wk, + 6wk, + 6 months.	SHAQ Depressed mood scale of IRGLI Illness cognitions (helplessnes, acceptance, disease benefits), Utrechtse coping list, patient satisfaction.	Significant improved helplessness, acceptance with small effect size. High patient satisfaction.

SHAQ=scleroderma health questionnaire, IRGL= Impact of Rheumatic Diseases on General Health and Lifestyle;

Reference List

(1) Medsger TA, Jr. 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(2):255-73, vi.

(2) Clements PJ, Lachenbruch PA, Seibold JR, Zee B, Steen VD, Brennan P et al. Skin thickness score in systemic sclerosis: an assessment of interobserver variability in 3 independent studies. J Rheumatol 1993; 20(11):1892-6.

(3) Maricq HR, Harper FE, Khan MM, Tan EM, LeRoy EC. Microvascular abnormalities as possible predictors of disease subsets in Raynaud phenomenon and early connective tissue disease. Clin Exp Rheumatol 1983; 1(3):195-205.

(4) Cutolo M, Sulli A, Pizzorni C, Accardo S. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. J Rheumatol 2000; 27(1):155-60.

(5) Sulli A, Pizzorni C, Smith V, Zampogna G, Ravera F, Cutolo M. Timing of transition between capillaroscopic patterns in systemic sclerosis. Arthritis Rheum 2012; 64(3):821-5.

(6) Ingegnoli F, Ardoino I, Boracchi P, Cutolo M. Nailfold capillaroscopy in systemic sclerosis: data from the EULAR scleroderma trials and research (EUSTAR) database. Microvasc Res 2013; 89:122-8. doi: 10.1016/j.mvr.2013.06.003. Epub;%2013 Jun 17.:122-8.

(7) Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980; 23(5):581-90.

(8) Lonzetti LS, Joyal F, Raynauld JP, Roussin A, Goulet JR, Rich E et al. Updating the American College of Rheumatology preliminary classification criteria for systemic sclerosis: addition of severe nailfold capillaroscopy abnormalities markedly increases the sensitivity for limited scleroderma. Arthritis Rheum 2001; 44(3):735-6.

(9) LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Jr. et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988; 15(2):202-5.

(10) Barnett AJ, Miller M, Littlejohn GO. The diagnosis and classification of scleroderma (systemic sclerosis). Postgrad Med J 1988; 64(748):121-5.

(11) van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A et al. 2013 Classification Criteria for Systemic Sclerosis: An American College of Rheumatology/ European League Against Rheumatism Collaborative Initiative. Arthritis Rheum 2013;NA.

(12) Nihtyanova SI, Denton CP. Autoantibodies as predictive tools in systemic sclerosis. Nat Rev Rheumatol 2010; 6(2):112-6.

(13) Reveille JD, Solomon DH. Evidence-based guidelines for the use of immunologic tests: anticentromere, Scl-70, and nucleolar antibodies. Arthritis Rheum 2003; 49(3):399-412.

(14) Vonk MC, Broers B, Heijdra YF, Ton E, Snijder R, van Dijk AP et al. Systemic sclerosis and its pulmonary complications in The Netherlands: an epidemiological study. Ann Rheum Dis 2009; 68(6):961-5.

(15) Hoffmann-Vold AM, Midtvedt O, Molberg O, Garen T, Gran JT. Prevalence of systemic sclerosis in south-east Norway. Rheumatology (Oxford) 2012; 51(9):1600-5.

(16) Allcock RJ, Forrest I, Corris PA, Crook PR, Griffiths ID. A study of the prevalence of systemic sclerosis in northeast England. Rheumatology (Oxford) 2004; 43(5):596-602.

(17) Le G, V, Mahr A, Mouthon L, Jeanneret D, Carzon M, Guillevin L. Prevalence of systemic sclerosis in a French multi-ethnic county. Rheumatology (Oxford) 2004; 43(9):1129-37.

(18) Arias-Nunez MC, Llorca J, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Filloy JA, Martin J et al. Systemic sclerosis in northwestern Spain: a 19-year epidemiologic study. Medicine (Baltimore) 2008; 87(5):272-80.

(19) Mayes MD, Lacey JV, Jr., Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum 2003; 48(8):2246-55.

(20) Steen VD, Oddis CV, Conte CG, Janoski J, Casterline GZ, Medsger TA, Jr. Incidence of systemic sclerosis in Allegheny County, Pennsylvania. A twenty-year study of hospital-diagnosed cases, 1963-1982. Arthritis Rheum 1997; 40(3):441-5.

(21) Furst DE, Fernandes AW, Iorga SR, Greth W, Bancroft T. Epidemiology of systemic sclerosis in a large US managed care population. J Rheumatol 2012; 39(4):784-6.

(22) Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2012; 51(6):1017-26.

(23) Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010; 69(10):1809-15.

(24) Nihtyanova SI, Tang EC, Coghlan JG, Wells AU, Black CM, Denton CP. Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study. QJM 2010; 103(2):109-15.

(25) Al-Dhaher FF, Pope JE, Ouimet JM. Determinants of morbidity and mortality of systemic sclerosis in Canada. Semin Arthritis Rheum 2010; 39(4):269-77.

(26) Kahan A, Coghlan G, McLaughlin V. Cardiac complications of systemic sclerosis. Rheumatology (Oxford) 2009; 48 Suppl 3:iii45-8. doi: 10.1093/rheumatology/kep110.:iii45-iii48.

(27) Allanore Y, Meune C, Vonk MC, Airo P, Hachulla E, Caramaschi P et al. Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of patients with systemic sclerosis. Ann Rheum Dis 2010; 69(1):218-21.

(28) Domsic RT, Rodriguez-Reyna T, Lucas M, Fertig N, Medsger TA, Jr. Skin thickness progression rate: a predictor of mortality and early internal organ involvement in diffuse scleroderma. Ann Rheum Dis 2011; 70(1):104-9.

(29) Manno RL, Wigley FM, Gelber AC, Hummers LK. Late-age onset systemic sclerosis. J Rheumatol 2011; 38(7):1317-25.

(30) Mizuno R, Fujimoto S, Saito Y, Nakamura S. Cardiac Raynaud's phenomenon induced by cold provocation as a predictor of long-term left ventricular dysfunction and remodelling in systemic sclerosis: 7-year follow-up study. Eur J Heart Fail 2010; 12(3):268-75.

(31) Follansbee WP, Miller TR, Curtiss EI, Orie JE, Bernstein RL, Kiernan JM et al. A controlled clinicopathologic study of myocardial fibrosis in systemic sclerosis (scleroderma). J Rheumatol 1990; 17(5):656-62.

(32) Tzelepis GE, Kelekis NL, Plastiras SC, Mitseas P, Economopoulos N, Kampolis C et al. Pattern and distribution of myocardial fibrosis in systemic sclerosis: a delayed enhanced magnetic resonance imaging study. Arthritis Rheum 2007; 56(11):3827-36.

(33) Meune C, Avouac J, Wahbi K, Cabanes L, Wipff J, Mouthon L et al. Cardiac involvement in systemic sclerosis assessed by tissue-doppler echocardiography during routine care: A controlled study of 100 consecutive patients. Arthritis Rheum 2008; 58(6):1803-9.

(34) Blessberger H, Binder T. NON-invasive imaging: Two dimensional speckle tracking echocardiography: basic principles. Heart 2010; 96(9):716-22.

(35) Walker UA, Tyndall A, Czirjak L, Denton C, Farge-Bancel D, Kowal-Bielecka O et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 2007; 66(6):754-63.

(36) Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med 2002; 165(12):1581-6.

(37) Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R et al. Interpretative strategies for lung function tests. Eur Respir J 2005; 26(5):948-68.

(38) Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183(6):788-824.

(39) Steen VD, Conte C, Owens GR, Medsger TA, Jr. Severe restrictive lung disease in systemic sclerosis. Arthritis Rheum 1994; 37(9):1283-9.

(40) Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008; 177(11):1248-54.

(41) Schurawitzki H, Stiglbauer R, Graninger W, Herold C, Polzleitner D, Burghuber OC et al. Interstitial lung disease in progressive systemic sclerosis: high-resolution CT versus radiography. Radiology 1990; 176(3):755-9.

(42) Koh ET, Lee P, Gladman DD, Abu-Shakra M. Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. Br J Rheumatol 1996; 35(10):989-93.

(43) Rolla G, Colagrande P, Scappaticci E, Chiavassa G, Dutto L, Cannizzo S et al. Exhaled nitric oxide in systemic sclerosis: relationships with lung involvement and pulmonary hypertension. J Rheumatol 2000; 27(7):1693-8.

(44) McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; 126(1 Suppl):14S-34S.

(45) Williams MH, Handler CE, Akram R, Smith CJ, Das C, Smee J et al. Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hypertension. Eur Heart J 2006; 27(12):1485-94.

(46) Chung L, Domsic RT, Lingala B, Alkassab F, Bolster M, Csuka ME et al. Survival and predictors of mortality in systemic sclerosis associated pulmonary arterial hypertension: Outcomes from the PHAROS registry. Arthritis Care Res (Hoboken) 2013;10.

(47) Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006; 173(9):1023-30.

(48) Steen VD, Graham G, Conte C, Owens G, Medsger TA, Jr. Isolated diffusing capacity reduction in systemic sclerosis. Arthritis Rheum 1992; 35(7):765-70.

(49) Sacks DG, Okano Y, Steen VD, Curtiss E, Shapiro LS, Medsger TA, Jr. Isolated pulmonary hypertension in systemic sclerosis with diffuse cutaneous involvement: association with serum anti-U3RNP antibody. J Rheumatol 1996; 23(4):639-42.

(50) Humbert M, Yaici A, de GP, Montani D, Sitbon O, Launay D et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. Arthritis Rheum 2011; 63(11):3522-30.

(51) Galie N, Rubin L, Hoeper M, Jansa P, Al-Hiti H, Meyer G et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. Lancet 2008; 371(9630):2093-100.

(52) Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009; 34(6):1219-63.

(53) Khanna D, Gladue H, Channick R, Chung L, Distler O, Furst DE et al. Recommendations for screening and detection of connective-tissue disease associated pulmonary arterial hypertension. Arthritis Rheum 2013;10.

(54) Coghlan JG, Denton CP, Grunig E, Bonderman D, Distler O, Khanna D et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2013.

(55) Shanmugam VK, Steen VD. Renal disease in scleroderma: an update on evaluation, risk stratification, pathogenesis and management. Curr Opin Rheumatol 2012; 24(6):669-76.

(56) Nikpour M, Hissaria P, Byron J, Sahhar J, Micallef M, Paspaliaris W et al. Prevalence, correlates and clinical usefulness of antibodies to RNA polymerase III in systemic sclerosis: a cross-sectional analysis of data from an Australian cohort. Arthritis Res Ther 2011; 13(6):R211.

(57) Guillevin L, Berezne A, Seror R, Teixeira L, Pourrat J, Mahr A et al. Scleroderma renal crisis: a retrospective multicentre study on 91 patients and 427 controls. Rheumatology (Oxford) 2012; 51(3):460-7.

(58) Steen VD, Medsger TA, Jr. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis Rheum 1998; 41(9):1613-9.

(59) Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis 2007; 66(7):940-4.

(60) Walker KM, Pope J. Treatment of systemic sclerosis complications: what to use when first-line treatment fails--a consensus of systemic sclerosis experts. Semin Arthritis Rheum 2012; 42(1):42-55.

(61) D'Angelo WA, Fries JF, Masi AT, Shulman LE. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. Am J Med 1969; 46(3):428-40.

(62) Sjogren RW. Gastrointestinal motility disorders in scleroderma. Arthritis Rheum 1994; 37(9):1265-82.

(63) Ebert EC. Gastric and enteric involvement in progressive systemic sclerosis. J Clin Gastroenterol 2008; 42(1):5-12.

(64) Clements PJ, Furst DE. Cutaneous involvement in Systemic Sclerosis. Systemic Sclerosis. 2 ed. 2004. 129-49.

(65) Avouac J, Clements PJ, Khanna D, Furst DE, Allanore Y. Articular involvement in systemic sclerosis. Rheumatology (Oxford) 2012; 51(8):1347-56.

(66) Salliot C, Mouthon L, Ardizzone M, Sibilia J, Guillevin L, Gottenberg JE et al. Sjogren's syndrome is associated with and not secondary to systemic sclerosis. Rheumatology (Oxford) 2007; 46(2):321-6.

(67) Bhadauria S, Moser DK, Clements PJ, Singh RR, Lachenbruch PA, Pitkin RM et al. Genital tract abnormalities and female sexual function impairment in systemic sclerosis. Am J Obstet Gynecol 1995; 172(2 Pt 1):580-7.

(68) Ostojic P, Damjanov N. The impact of depression, microvasculopathy, and fibrosis on development of erectile dysfunction in men with systemic sclerosis. Clin Rheumatol 2007; 26(10):1671-4.

(69) Hudson M, Thombs BD, Steele R, Panopalis P, Newton E, Baron M. Health-related quality of life in systemic sclerosis: a systematic review. Arthritis Rheum 2009; 61(8):1112-20.

(70) Thombs BD, Taillefer SS, Hudson M, Baron M. Depression in patients with systemic sclerosis: a systematic review of the evidence. Arthritis Rheum 2007; 57(6):1089-97.

(71) Thombs BD, Hudson M, Taillefer SS, Baron M. Prevalence and clinical correlates of symptoms of depression in patients with systemic sclerosis. Arthritis Rheum 2008; 59(4):504-9.

(72) Matsuura E, Ohta A, Kanegae F, Haruda Y, Ushiyama O, Koarada S et al. Frequency and analysis of factors closely associated with the development of depressive symptoms in patients with scleroderma. J Rheumatol 2003; 30(8):1782-7.

(73) Haythornthwaite JA, Heinberg LJ, McGuire L. Psychologic factors in scleroderma. Rheum Dis Clin North Am 2003; 29(2):427-39.

(74) Joachim G, Acorn S. Life with a rare chronic disease: the scleroderma experience. J Adv Nurs 2003; 42(6):598-606.

(75) van Lankveld WG, Vonk MC, Teunissen H, van den Hoogen FH. 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 (Oxford) 2007; 46(5):872-6.

(76) Beretta L, Santaniello A, Lemos A, Masciocchi M, Scorza R. Validity of the Saint George's Respiratory Questionnaire in the evaluation of the health-related quality of life in patients with interstitial lung disease secondary to systemic sclerosis. Rheumatology (Oxford) 2007; 46(2):296-301.

(77) Khanna D, Hays RD, Maranian P, Seibold JR, Impens A, Mayes MD et al. Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. Arthritis Rheum 2009; 61(9):1257-63.

(78) Rosato E, Gigante A, Barbano B, Cianci R, Molinaro I, Rossi C et al. Intrarenal hemodynamic parameters correlate with glomerular filtration rate and digital microvascular damage in patients with systemic sclerosis. Semin Arthritis Rheum 2012; 41(6):815-21.

(79) Mouthon L, Rannou F, Berezne A, Pagnoux C, Arene JP, Fois E et al. Development and validation of a scale for mouth handicap in systemic sclerosis: the Mouth Handicap in Systemic Sclerosis scale. Ann Rheum Dis 2007; 66(12):1651-5.

(80) Rannou F, Poiraudeau S, Berezne A, Baubet T, Le-Guern V, Cabane J et al. Assessing disability and quality of life in systemic sclerosis: construct validities of the Cochin Hand Function Scale, Health Assessment Questionnaire (HAQ), Systemic Sclerosis HAQ, and Medical Outcomes Study 36-Item Short Form Health Survey. Arthritis Rheum 2007; 57(1):94-102.

(81) Merkel PA, Herlyn K, Martin RW, Anderson JJ, Mayes MD, Bell P et al. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. Arthritis Rheum 2002; 46(9):2410-20.

(82) Johnson SR, Hawker GA, Davis AM. The health assessment questionnaire disability index and scleroderma health assessment questionnaire in scleroderma trials: an evaluation of their measurement properties. Arthritis Rheum 2005; 53(2):256-62.

(83) Smyth AE, MacGregor AJ, Mukerjee D, Brough GM, Black CM, Denton CP. A cross-sectional comparison of three self-reported functional indices in scleroderma. Rheumatology (Oxford) 2003; 42(6):732-8.
(84) Kwakkenbos L, van den Hoogen FH, Custers J, Prins J, Vonk MC, van Lankveld WG et al. Validity of the Fear of Progression Questionnaire-Short Form in patients with systemic sclerosis. Arthritis Care Res (Hoboken) 2012; 64(6):930-4.
(85) Heinberg LJ, Kudel I, White B, Kwan A, Medley K, Wigley F et al. Assessing body image in patients with systemic sclerosis (scleroderma): validation of the adapted Satisfaction with Appearance Scale. Body Image 2007; 4(1):79-86.
(86) Malcarne VL, Hansdottir I, McKinney A, Upchurch R, Greenbergs HL, Henstorf GH et al. Medical signs and symptoms associated with disability, pain, and psychosocial adjustment in systemic sclerosis. J Rheumatol 2007; 34(2):359-67.
(87) Kallen MA, Mayes MD, Kriseman YL, de Achaval SB, Cox VL, Suarez-Almazor ME. The symptom burden index: development and initial findings from use with patients with systemic sclerosis. J Rheumatol 2010; 37(8):1692-8.
(88) Sandqvist G, Eklund M, Akesson A, Nordenskiold U. Daily activities and hand function in women with scleroderma. Scand J Rheumatol 2004; 33(2):102-7.
(89) Balbir-Gurman A, Braun-Moscovici Y. Scleroderma - new aspects in pathogenesis and treatment. Best Pract Res Clin Rheumatol 2012; 26(1):13-24.
(90) Nihtyanova SI, Brough GM, Black CM, Denton CP. Mycophenolate mofetil in diffuse cutaneous systemic sclerosis--a retrospective analysis. Rheumatology (Oxford) 2007; 46(3):442-5.
(91) Smith V, Van Praet JT, Vandooren B, Van der Cruyssen B, Naeyaert JM, Decuman S et al. Rituximab in diffuse cutaneous systemic sclerosis: an open-label clinical and histopathological study. Ann Rheum Dis 2010; 69(1):193-7.
(92) Daoussis D, Liossis SN, Tsamandas AC, Kalogeropoulou C, Kazantzi A, Sirinian C et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology (Oxford) 2010; 49(2):271-80.
(93) Vonk MC, Marjanovic Z, van den Hoogen FH, Zohar S, Schattenberg AV, Fibbe WE et al. Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis. Ann Rheum Dis 2008; 67(1):98-104.
(94) Poole JL. Musculoskeletal rehabilitation in the person with scleroderma. Curr Opin Rheumatol 2010; 22(2):205-12.
(95) Samuelson UK, Ahlmen EM. Development and evaluation of a patient education program for persons with systemic sclerosis (scleroderma). Arthritis Care Res 2000; 13(3):141-8.
(96) Genth E, Baltscheit C. [Patient education “systemic sclerosis”]. Z Rheumatol 2003; 62(Suppl 2):II24-II25.
(97) world health organisation. International Classification of Functioning, Disability and Health: ICF. 2001. Ref Type: Report
(98) Stamm TA, Mattsson M, Mihai C, Stocker J, Binder A, Bauernfeind B et al. Concepts of functioning and health important to people with systemic sclerosis: a qualitative study in four European countries. Ann Rheum Dis 2011; 70(6):1074-9.
(99) Stucki G, Cieza A, Geyh S, Battistella L, Lloyd J, Symmons D et al. ICF Core Sets for rheumatoid arthritis. J Rehabil Med 2004;(44 Suppl):87-93.
(100) Saketkoo LA, Escorpizo R, Keen KJ, Fligelstone K, Distler O. International Classification of Functioning, Disability and Health Core Set construction in systemic sclerosis and other rheumatic diseases: a EUSTAR initiative. Rheumatology (Oxford) 2012; 51(12):2170-6.

(101) Clements PJ, Allanore Y, Khanna D, Singh M, Furst DE. Arthritis in systemic sclerosis: systematic review of the literature and suggestions for the performance of future clinical trials in systemic sclerosis arthritis. Semin Arthritis Rheum 2012; 41(6):801-14.
(102) Blom-Bulow B, Jonson B, Bauer K. Factors limiting exercise performance in progressive systemic sclerosis. Semin Arthritis Rheum 1983; 13(2):174-81.
(103) Poole JL, Steen VD. The use of the Health Assessment Questionnaire (HAQ) to determine physical disability in systemic sclerosis. Arthritis Care Res 1991; 4(1):27-31.
(104) Richards HL, Herrick AL, Griffin K, Gwilliam PD, Loukes J, Fortune DG. Systemic sclerosis: patients’ perceptions of their condition. Arthritis Rheum 2003; 49(5):689-96.
(105) Nguyen C, Poiraudeau S, Mestre-Stanislas C, Rannou F, Berezne A, Papelard A et al. Employment status and socio-economic burden in systemic sclerosis: a cross-sectional survey. Rheumatology (Oxford) 2010; 49(5):982-9.
(106) Berezne A, Seror R, Morell-Dubois S, de MM, Fois E, Dzeing-Ella A et al. Impact of systemic sclerosis on occupational and professional activity with attention to patients with digital ulcers. Arthritis Care Res (Hoboken) 2011; 63(2):277-85.
(107) Allaire SH. Update on work disability in rheumatic diseases. Curr Opin Rheumatol 2001; 13(2):93-8.
(108) Mau W, Beyer W, Ehlebracht-Konig I, Engel M, Genth E, Greitemann B et al. [Burden of illness. First routine report on socio-medical consequences of inflammatory rheumatic disease in Germany]. Z Rheumatol 2008; 67(2):157-64.
(109) Sharif R, Mayes MD, Nicassio PM, Gonzalez EB, Draeger H, McNearney TA et al. Determinants of work disability in patients with systemic sclerosis: a longitudinal study of the GENISOS cohort. Semin Arthritis Rheum 2011; 41(1):38-47.
(110) Hudson M, Steele R, Lu Y, Thombs BD, Baron M. Work disability in systemic sclerosis. J Rheumatol 2009; 36(11):2481-6.
(111) Bernatsky S, Panopolis P, Hudson M, Pope J, Leclercq S, Robinson D et al. Demographic and clinical factors associated with physician service use in systemic sclerosis. J Rheumatol 2009; 36(1):96-8.
(112) Minier T, Pentek M, Brodszky V, Ecseki A, Karpati K, Polgar A et al. Cost-of-illness of patients with systemic sclerosis in a tertiary care centre. Rheumatology (Oxford) 2010; 49(10):1920-8.
(113) Furst DE, Fernandes AW, Iorga SR, Greth W, Bancroft T. Annual medical costs and healthcare resource use in patients with systemic sclerosis in an insured population. J Rheumatol 2012; 39(12):2303-9.
(114) Johnson SR, Carette S, Dunne JV. Scleroderma: health services utilization from patients’ perspective. J Rheumatol 2006; 33(6):1123-7.
(115) Rubenzik TT, Derk CT. Unmet patient needs in systemic sclerosis. J Clin Rheumatol 2009; 15(3):106-10.
(116) Teunissen HA, van Lankveld W, Vonk MC, van den Hoogen F. Systemische sclerose: de gevolgen voor het psychisch en lichamelijk functioneren, en de behoefte aan begeleiding. Nederlands Tijdschrift voor Reumatologie [4], 33-9. 2005.
(117) Askew LJ, Beckett VL, An KN, Chao EY. Objective evaluation of hand function in scleroderma patients to assess effectiveness of physical therapy. Br J Rheumatol 1983; 22(4):224-32.
(118) Sandqvist G, Akesson A, Eklund M. Evaluation of paraffin bath treatment in patients with systemic sclerosis. Disabil Rehabil 2004; 19;26(16):981-7.
(119) Mancuso T, Poole JL. The effect of paraffin and exercise on hand function in persons with scleroderma: a series of single case studies. J Hand Ther 2009; 22(1):71-7.

(120) Mugii N, Hasegawa M, Matsushita T, Kondo M, Orito H, Yanaba K et al. The efficacy of self-administered stretching for finger joint motion in Japanese patients with systemic sclerosis. J Rheumatol 2006; 33(8):1586-92.
(121) Maddali BS, Del RA, Galluccio F, Tai G, Sigismondi F, Passalacqua M et al. Efficacy of a tailored rehabilitation program for systemic sclerosis. Clin Exp Rheumatol 2009; 27(3 Suppl 54):44-50.
(122) Bongi SM, Del RA, Galluccio F, Sigismondi F, Miniati I, Conforti ML et al. Efficacy of connective tissue massage and Mc Mennell joint manipulation in the rehabilitative treatment of the hands in systemic sclerosis. Clin Rheumatol 2009; 28(10):1167-73.
(123) Seeger MW, Furst DE. Effects of splinting in the treatment of hand contractures in progressive systemic sclerosis. Am J Occup Ther 1987; 41(2):118-21.
(124) Antonioli CM, Bua G, Frige A, Prandini K, Radici S, Scarsi M et al. An individualized rehabilitation program in patients with systemic sclerosis may improve quality of life and hand mobility. Clin Rheumatol 2009; 28(2):159-65.
(125) Bongi SM, Del RA, Passalacqua M, Miccio S, Cerinic MM. Manual lymph drainage improving upper extremity edema and hand function in patients with systemic sclerosis in edematous phase. Arthritis Care Res (Hoboken) 2011; 63(8):1134-41.
(126) Naylor WP, Douglass CW, Mix E. The nonsurgical treatment of microstomia in scleroderma: a pilot study. Oral Surg Oral Med Oral Pathol 1984; 57(5):508-11.
(127) Pizzo G, Scardina GA, Messina P. Effects of a nonsurgical exercise program on the decreased mouth opening in patients with systemic scleroderma. Clin Oral Investig 2003; 7(3):175-8.
(128) Poole J, Conte C, Brewer C, Good CC, Perella D, Rossie KM et al. Oral hygiene in scleroderma: The effectiveness of a multi-disciplinary intervention program. Disabil Rehabil 2010; 32(5):379-84.
(129) Yuen HK, Marlow NM, Reed SG, Mahoney S, Summerlin LM, Leite R et al. Effect of orofacial exercises on oral aperture in adults with systemic sclerosis. Disabil Rehabil 2012; 34(1):84-9.
(130) Maddali-Bongi S, Landi G, Galluccio F, Del RA, Miniati I, Conforti ML et al. The rehabilitation of facial involvement in systemic sclerosis: efficacy of the combination of connective tissue massage, Kabat's technique and kinesitherapy: a randomized controlled trial. Rheumatol Int 2011; 31(7):895-901.
(131) Pinto AL, Oliveira NC, Gualano B, Christmann RB, Painelli VS, Artioli GG et al. Efficacy and safety of concurrent training in systemic sclerosis. J Strength Cond Res 2011; 25(5):1423-8.
(132) Oliveira NC, dos Santos Sabbag LM, de Sa Pinto AL, Borges CL, Lima FR. Aerobic exercise is safe and effective in systemic sclerosis. Int J Sports Med 2009; 30(10):728-32.
133) Buenaver LF, McGuire L, Haythornthwaite JA. Cognitive-Behavioral self-help for chronic pain. J Clin Psychol 2006; 62(11):1389-96.
(134) Kwakkenbos L, Bluyssen SJ, Vonk MC, van Helmond AF, van den Ende CH, van den Hoogen FH et al. Addressing patient health care demands in systemic sclerosis: pre-post assessment of a psycho-educational group programme. Clin Exp Rheumatol 2011; 29(2 Suppl 65):S60-S65.

CHAPTER 2

Left ventricular dysfunction assessed by speckle tracking strain analysis in Systemic Sclerosis patients: relationship with functional capacity and ventricular arrhythmias

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K.H. Yiu, A.A. Schouffoer, N. Ajmone Marsan, M.K. Ninaber, J. Stolk, T.P.M. Vliet-Vlieland, R.W. Scherptong, V. Delgado, E.R. Holman, H. Fat Tse, T.W.J. Huizinga, J.J. Bax, A.J.M. Schuerwegh.

* Kai Hang Yiu and Anne A. Schouffoer contributed equally to this work and should be considered as joint first authors

Abstract

Background: Systemic sclerosis is a connective tissue disease characterized by vascular inflammation and fibrosis. Visceral involvement, including cardiac manifestations can lead to severe clinical complications, such as congestive heart failure, arrhythmias and sudden death. Conventional echocardiography parameters have limited sensitivity to detect subtle myocardial dysfunction in patients with systemic sclerosis (SSc). The aim of the study was to assess, using novel speckle tracking strain analysis, the presence of myocardial dysfunction in SSc patients and to investigate its relationship with functional capacity and ventricular arrhythmias.

Methods: A total of 104 SSc patients (age 54 ± 12 yrs, 77% female) were included and underwent cardiopulmonary exercise testing, 24-hour electrocardiography Holter, and transthoracic echocardiography. For comparison purposes, 37 matched healthy controls were included.

Results: The total population consisted of 51 patients with limited SSc and 53 patients with diffuse SSc. Peak VO_2% predicted was 91 ± 20% and 28 patients had abnormal Holter findings (ventricular tachycardia or ventricular ectopics >100/day). Patients with SSc, as compared with controls, had impaired global longitudinal and circumferential strains (-18.2 ± 1.8% versus -21.3 ± 1.7% and -18.2 ± 2.3% versus -21.3 ± 2.1% respectively; each $p < 0.01$), but there was no difference in the left ventricular ejection fraction between patients and controls (63.5 ± 7.2% vs 64.6 ± 4.4%, p=0.20). In patients with SSc, global longitudinal (r=-0.46, $p<0.01$) and circumferential strains (r=-0.41, $p<0.01$) correlated with peak VO_2% predicted. Multivariate analysis showed that global longitudinal and circumferential strains were independently associated with peak VO_2% predicted. Compared to SSc patients with normal results on EKG Holter monitoring, SSc patients with abnormal results showed impaired global longitudinal strains (-18.5 ± 1.5% versus -17.1 ± 2.1%; $p <0.01$) and circumferential strains (-18.7 ± 2.0% versus -17.3 ± 2.5%; p=0.01), and each strain measure was independently associated with abnormal Holter findings

Conclusion: Speckle tracking strain analysis detected subtle myocardial dysfunction in SSc patients. Importantly, decreased global longitudinal and circumferential strains are associated with lower functional capacity and rhythm disturbances.

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by deposition of collagen in multiple organs and associated with significant disability and reduced life expectancy.[1] Cardiovascular involvement has been shown to be one of the leading causes of mortality in SSc[2] and to occur in up to 70% of patients as autoptic finding.[3] Early diagnosis and accurate staging of myocardial involvement are therefore crucial for the management of these patients and for therapeutic strategies.

Conventional echocardiographic assessment of left ventricular (LV) systolic function is based on the measure of LV ejection fraction (EF). This approach however showed limited sensitivity for the assessment of myocardial abnormalities in SSc patients, being able to identify only 5% of patients with cardiac involvement.[4] More sophisticated and sensitive techniques for the assessment of LV function are therefore needed to improve the detection of subclinical myocardial dysfunction in SSc patients. Initial studies using tissue Doppler imaging suggested that myocardial velocity and deformation (strain) might be more sensitive than conventional measures in identifying subtle cardiac dysfunction in asymptomatic SSc patients.[5-7] However, the clinical implications of this alternative approach for LV function assessment have not been evaluated.

Recently, two-dimensional (2D) speckle tracking analysis has been proposed as a sensitive and accurate method for the evaluation of subclinical myocardial dysfunction, providing measures of LV regional and global strain in three orthogonal directions (longitudinal, circumferential and radial).[8] The aim of this study was therefore to apply this novel technique to assess the presence of LV systolic dysfunction in a large cohort of SSc patients. Furthermore, the clinical value of the measurement of LV global strain by 2D speckle tracking analysis was evaluated in relation with functional capacity and ventricular arrhythmias in these patients.

Methods

Patient population and protocol

The current study included 113 consecutive patients with SSc referred to the department of Rheumatology, Leiden University Medical Center. The patients were recruited from two studies; a randomized controlled trial evaluating the effectiveness of a multidisciplinary team care program[9] and a study evaluating the outcomes of a two-days diagnostic multidisciplinary daycare program[10]. All patients underwent an extensive screening, including detailed physical examination, a Modified Rodnan Skin Score assessment,[11] laboratory testing (including erythrocyte sedimentation rate, anti-nuclear, anti-topoisomerase I, anti-RNP and anti-centromere antibodies assessments), chest X-ray and lung function test. Interstitial lung disease was diagnosed by chest X-ray and by lung function test, and with computed tomography scan when indicated.

Patients were classified as limited systemic sclerosis (lSSc) or diffuse systemic sclerosis (dSSc), according to the classification system described by LeRoy et al.[12] In addition, cardiopulmonary exercise (CPET) and 24-hour electrocardiography (ECG) Holter monitoring were performed to assess patient functional capacity and potential ventricular arrhythmias, respectively. None of the patients had angina pectoris or symptoms attributable to cardiovascular disease and therefore specific tests for microvascular and macrovascular ischemia were not performed. Transthoracic echocardiography was performed to evaluate conventional parameters of cardiac function and to assess subclinical LV systolic dysfunction using novel speckle tracking analysis. The relationship of LV function with functional capacity and ventricular arrhythmias was evaluated.

Seven patients were not able to perform CPET (because of severe pulmonary hypertension in 4 patients, severe aortic valve stenosis in 1 patient and severe SSc disease status in 2 patients) and therefore excluded from the analysis. In addition, 2 patients were excluded because of an incomplete clinical assessment. The final study population consisted of 104 patients.

For comparison purposes, 37 normal individuals (1:3 ratio with SSc patients) matched for age and gender were included as a control group. These subjects were referred for atypical chest pain, palpitations, or syncope without murmur and showed normal structural heart on echocardiography.

The study protocol was approved by the Ethics Committee of the Leiden University Medical Center. All participants provided written informed consent for the studies in which they participated

Lung function test

Lung function test was performed in all SSc patients and included spirometry and single breath diffusion lung capacity for carbon monoxide (DLCO). Spirometry measurements included forced vital capacity (FVC) and total lung capacity (TLC) measured according to the American Thoracic Society/European Respiratory Society recommendations[13-15] and expressed as percentage predicted.

Conventional echocardiography

All SSc patients and controls were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid 7, General Electric Vingmed Ultrasound, Milwaukee, USA). Images were obtained using a 3.5-MHz transducer and digitally stored in cine-loop format; offline analysis was performed using EchoPAC version 108.1.5 (General Electric - Vingmed, Horten, Norway). LV dimensions, volumes and EF were measured according to the current recommendations.[16] Evaluation of LV diastolic function was based on the pulsed-wave Doppler of mitral valve inflow as recommended by the American Society of Echocardiography,[17] measuring peak early

diastolic velocity (E), peak late (A) diastolic velocity, their ratio (E/A) and the E wave deceleration. Pulmonary venous flow velocities during systole (S) and diastole (D) were also recorded. Using tissue Doppler imaging, the early diastolic velocity (E`) and systolic velocity (S`) was measured at the level of the LV basal lateral segment. In addition, E/E` ratio was calculated as an estimation of LV filling pressure.[18] LV diastolic dysfunction was therefore categorized as previously described: normal; mild, defined as LV impaired relaxation without evidence of increased filling pressure; moderate, defined as LV impaired relaxation associated with moderate elevation of filling pressures or pseudo-normal filling; and severe, defined as restrictive LV filling.[17] Pulmonary arterial systolic pressure (PASP) was estimated by right ventricular systolic pressure, which was calculated from the tricuspid regurgitation peak gradient using Bernoulli equation, and adding right atrial pressure estimated by the dimension and the degree of inferior vena cava respiratory collapse.[19]

Two-dimensional speckle tracking strain analysis

Two-dimensional speckle tracking analysis is a novel imaging technique which allows the assessment of LV myocardial deformation by tracking natural acoustic markers (speckles) in a frame-to-frame basis within the cardiac cycle. The speckles are visible in the standard gray-scale 2D images and are equally distributed within the myocardium. As represented in Figure 1, LV deformation can be assessed in three orthogonal directions as longitudinal, circumferential and radial strain.[20]

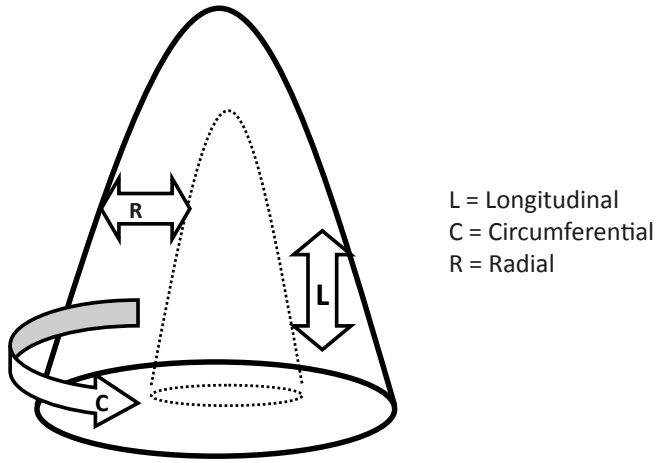
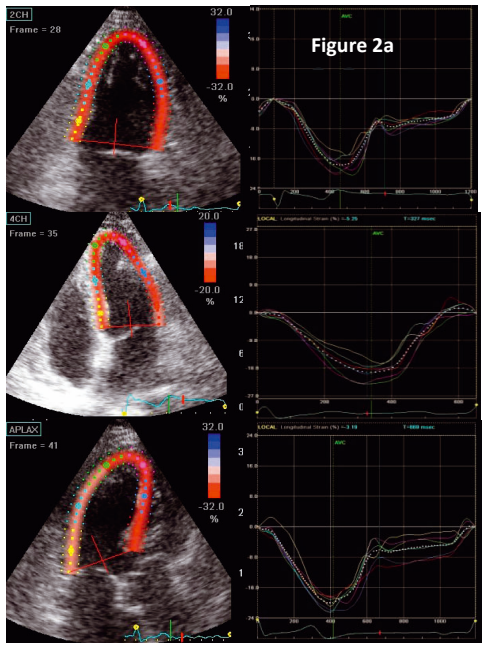


Figure 1: Schematic representations of the three orthogonal directions of strain measured with two-dimensional speckle tracking analysis. Global longitudinal strain evaluates the shortening/lengthening of the myocardial wall. Radial strain evaluates the thickening and thinning of the myocardial wall and circumferential strain asses the shortening/lengthening along the curvature of the LV.



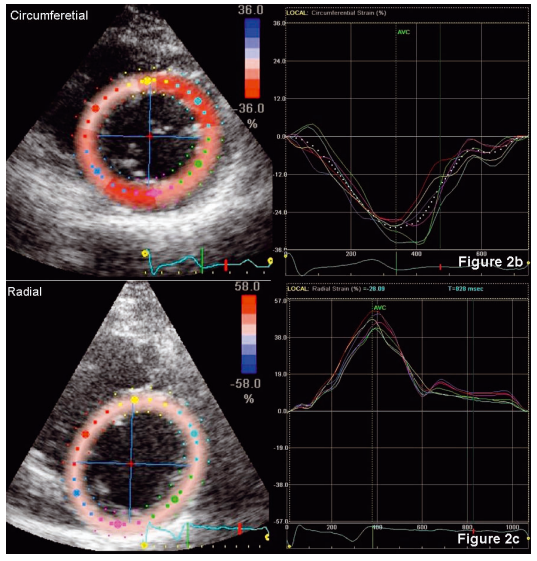


Figure 2: Left ventricular strain assessment in 3 orthogonal directions by two-dimensional speckle tracking analysis. Figure 2a illustrates the calculation of global longitudinal strain from the apical 4-chamber, 2-chamber and the long-axis views. Each color line denotes regional segmental strain (6 segments per views, for a total of 18 segments) and the white dotted line represents the average strain value of each view. The global longitudinal strain is calculated by the average of peak strain in the three apical views. From the mid-ventricular short-axis view of the LV, global circumferential (Figure 2b) and radial (Figure 2c) strains are calculated by averaging the peak strain of six LV segments.

Longitudinal strain, evaluating the shortening/lengthening of the myocardial wall, was measured from the 3 apical views: 2-chamber view (including anterior and inferior walls), 4- chamber view (posteroseptal and lateral walls) and long axis view (anteroseptal and posterior walls). Each wall was divided into 3 levels (basal, mid and apical) and subsequently 18 segmental strain curves were obtained. Global longitudinal strain was calculated as the average of peak systolic strain values of the 18 segments (Figure 2a).
From LV mid-ventricular short-axis view, circumferential strain (evaluating myocardial shortening/lengthening along LV curvature) and radial strain (evaluating myocardial thickening/thinning) were measured. The global values of circumferential and radial strains were derived from the average of peak systolic strain values of 6 segments, as illustrated in Figure 2b and 2c, respectively. Global longitudinal and circumferential strains are expressed as negative values, and a lower strain is represented by less negative values. Global radial strain is expressed as positive values, and lower values indicate lower strain.
The intra- and inter-observer agreement for the measurements of longitudinal, circumferential and radial strains have been reported previously.[20]

Cardiopulmonary exercise testing

All SSc patients performed a maximal exercise stress test on an electrically braked stationary cycle ergometer using a ramp protocol according to the American Thoracic Society/American College of Chest Physician statement on cardiopulmonary testing.[21] Briefly, a tight fitting facemask was worn by the patients and allowed ventilation and metabolic gas exchange measurements (Oxycon Pro, Jaeger-Viasys Healthcare, Hoechberg, Germany). The initial work load was 30W, with further increment of 5W every 30 seconds. Patients were encouraged to exercise until exhaustion or until supervising physician stopped the test because of significant symptoms, such as chest pain, dizziness, ST-segment deviations, or marked systolic hypotension or hypertension. Peak VO_2 was defined as the highest oxygen consumption during any stage of maximal exercise. Furthermore, peak VO_2 was adjusted to age, gender and weight and expressed as percentage predicted.

24-hour electrocardiography Holter monitoring

A 24-hour ECG Holter monitoring was performed in 100 out of 104 patients to detect potential ventricular arrhythmias. Abnormal Holter results were defined as the presence of intermittent bundle branch block, ventricular arrhythmias including frequent monomorphic and/or polymorphic premature ventricular contractions >100 per day, or non-sustained or sustained ventricular tachycardia.[22]

Table 1: Clinical characteristics of the 104 patients with systemic sclerosis (SSc) and comparison between patients with limited systemic sclerosis (lSSc) and diffuse systemic sclerosis (dSSc).

	SSc (n=104)	lSSc (n=51)	dSSc (n=53)	p value
Age (yrs)	54±12	58±12	50±12	**<0.01**
Female gender, n (%)	80(77)	43(84)	37(70)	0.08
Time since diagnosis, yrs	5.1±2.3	7.1±3.5	4.1±2.5	**<0.01**
Time since onset of Raynaud's, yrs	8.6±6.3	15.0±5.8	5.8±4.2	**<0.01**
Time since onset of skin manifestation, yrs	5.6 ±3.5	7.1 ±6.2	4.7 ±2.8	**0.02**
Modified Rodnan Skin Score	5.6±6.1	2.8±2.2	8.3±7.4	**<0.01**
Systolic blood pressure, mmHg	122±18	125±18	119±18	0.08
Diastolic blood pressure, mmHg	71±9	70±8	72±11	0.23
Systemic hypertension	11(11)	2(18)	9(82)	**0.03**
ESR, mm/hr	20.5±17.6	20.7±19.8	20.3±15.4	0.91
Immune markers:				
Anti-nuclear, n (%)	94(90)	46(90)	48(91)	0.61
Anti-topoisomerase, n (%)	36(35)	7(14)	29 (58)	**<0.01**
Anti-centromere, n (%)	25(24)	21(41)	4(7)	**<0.01**
Anti-RNP, n (%)	7(7)	5(10)	2(4)	0.38
Interstitial lung disease, n (%)	49(47)	15(28)	34(64)	**<0.01**
Pulmonary hypertension	4(4)	1(2)	3(6)	0.62
*Chronic kidney disease	10(10)	6(12)	4(8)	0.52
Lung function:				
FVC% predicted	94.4±14.4	94.9±12.4	93.9±15.9	0.73
TLC% predicted	86.9±18.1	92.7±17.2	82.1±17.5	**<0.01**
DLCO% predicted	63.3±16.8	65.4±17.5	61.2±16.1	0.22
Current immunosuppressive medication (%):				
Corticosteroids, n (%)	15 (14)	6 (12)	9 (17)	0.45
Methotrexate, n (%)	4 (8)	3(6)	4 (8)	0.52
Azathioprine, n (%)	2 (4)	4 (8)	2 (4)	0.32
Current cardiovascular medications (%):				
Calcium antagonists, n (%)	46 (44)	17 (33)	29 (55)	0.03
ACE inhibitors, n (%)	42 (40)	12 (24)	30 (57)	<0.01

Abbreviations: ACE = Angiotensin converting-enzyme; dSSc= Diffuse systemic sclerosis; DLCO = Diffusion lung capacity for carbon monoxide; ESR = Erythrocyte sedimentation rate; FVC = Forced vital capacity; TLC = Total lung capacity. *Chronic kidney disease was defined as an estimated glomerular filtration clearance rate < 60ml/min/1,73m^2 for more than 3 months

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Categorical data are presented as frequencies and percentages. Continuous variables were tested for normal distribution with the Kolmogorov-Smirnov test. Statistical comparisons were performed by using Student's t test for continuous variables, and chi square test for binary variables. Univariate linear regression analysis was used to identify potential determinants of peak VO_2% predicted. Correlations were expressed in terms of Pearson's correlation coefficient. Moreover, univariate binary logistic regression was used to determine the factors associated (using odd ratios (OR) and confidence intervals (CI)) with abnormal Holter results. The final multivariate models for peak VO_2% predicted and abnormal Holter results were obtained using the enter method by including parameters that were statistically significant in univariate analysis. To avoid bias from multicollinearity, multi-directional global strains were entered to the step-wise model individually. Analysis of covariance tests with inclusion of covariates to correct for significant different variables of subpopulation characteristics were performed. All statistical analysis were performed using the statistical package SPSS for windows (Version 15.0, SPSS, Chicago, USA). A p value <0.05 was considered to be statistically significant.

Results

Clinical characteristics of the patient population

A total of 51 (49%) patients were classified as having lSSc and 53 (51%) patients as having dSSc. Clinical characteristics of the total population and of the 2 subtypes of SSc (limited and diffuse) are shown in Table 1. According to the matching criteria, age (54±10 vs. 54±12, p=0.82) and gender (female 77% vs. 73%, p=0.66) were similar between SSc patients and controls. Most of SSc patients were positive for antinuclear antibodies and approximately 50% had underlying interstitial lung disease. In addition, 24 patients (20 dSSc patients and 4 lSSc patients) received a treatment with cyclophosphamide, and 13 patients (all dSSC) stem cell transplantation. A total of 4 patients had mild pulmonary hypertension (2 due to underlying interstitial lung disease and 2 due to pulmonary arterial hypertension), 1 patient had a previous myocardial infarction and 2 patients were known for epicardial coronary artery disease successfully revascularised by coronary artery bypass grafting.

Patients with dSSc were associated with a younger age, shorter time since diagnosis and time since onset of Raynaud's phenomenon and skin manifestation. Moreover, patients with dSSc were more likely to have systemic hypertension, underlying interstitial lung disease, lower TLC% predicted and to receive angiotensin-converting enzyme inhibitors (mainly to prevent renal crisis) as compared to patients with lSSc. Patients with lSSc had a significantly lower prevalence of anti-topoisomerase antibodies and a lower modified Rodnan skin score.

Table 2: Conventional echocardiographic parameters and two-dimensional speckle tracking strain measurements in patients with systemic sclerosis (SSc) versus controls and in patients with limited (lSSc) versus diffuse (dSSc) systemic sclerosis.

	Controls (n=37)	SSc (n=104)	p value	lSSc (n=51)	dSSc (n=53)	p value
Conventional echocardiographic parameters						
LV end diastolic volume (ml)	70.6±20.6	76.0±25.4	0.21	72.9±22.4	78.9±23.0	0.24
LV end systolic volume (ml)	26.6±5.7	29.1±13.1	0.13	28.8±13.9	29.4±12.5	0.82
LV ejection fraction (%)	64.6±4.4	63.5±7.2	0.20	64.6±7.9	63.4±6.4	0.19
PASP (mmHg)	21.7±6.3	28.9±8.7	**<0.01**	29.5±8.3	28.3±9.1	0.48
LV diastolic function, n (%)						
Normal	21 (62)	35 (34)	**<0.01**	18 (35)	17 (32)	0.62
Mild	9 (24)	24 (23)		12 (24)	12 (23)	
Moderate	5 (14)	30 (29)		16 (31)	14 (26)	
Severe	0 (0)	15 (14)		5 (10)	10 (19)	
E` velocity (cm/s)	9.8±2.0	8.5±2.8	**0.03**	8.8±2.7	8.1±3.0	0.22
E/E` ratio	7.7±1.9	10.1±3.8	**<0.01**	10.2±3.8	10.0±3.7	0.73
S` velocity (cm/s)	6.4±1.4	6.3±2.1	0.81	6.8±2.0	5.7±2.0	**<0.01**
Speckle tracking analysis						
Global longitudinal strain (%)	-21.3±1.7	-18.2±1.8	**<0.01**	-18.6±1.6	-17.9±1.9	**0.02**
Global circumferential strain (%)	-21.3±2.1	-18.2±2.3	**<0.01**	-19.0±2.0	-17.5±2.3	**<0.01**
Global radial strain (%)	40.3±12.4	37.0±13.9	0.18	37.6±13.1	36.3±14.7	0.65

Abbreviations: LV= Left ventricular; PASP= Pulmonary arterial systolic pressure; E = Early; A = Late; E`= Early diastolic velocity at basal mitral annulus; For other abbreviations, see Table 1.

Echocardiographic characteristics of the patient population

Conventional echocardiographic parameters of LV systolic and diastolic function of SSc patients and controls are shown in Table 2. No significant differences were noted in LV volumes and EF between SSc patients and controls (Table 2). Moreover, S` velocity derived from tissue Doppler imaging was similar to controls. However, estimated PASP was significantly higher in SSc patients as compared to controls and E/E` ratio and LV diastolic dysfunction grade were significantly worse. When comparing the 2 different subtypes of SSc, both groups showed similar values of conventional echocardiographic parameters.

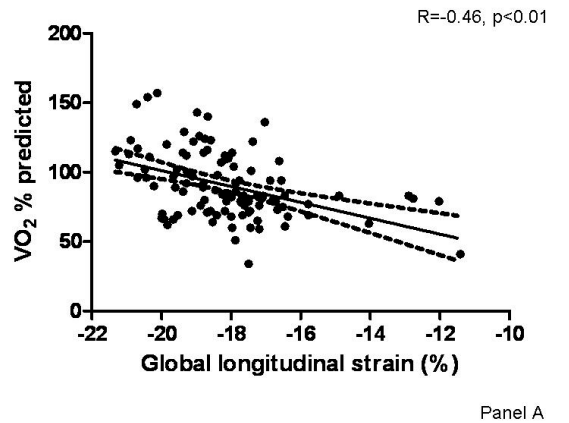
In order to detect subtle LV dysfunction, myocardial strain values in three orthogonal directions were measured by speckle tracking analysis (Table 2). Both global longitudinal and circumferential strains were significantly impaired in SSc patients as compared to controls. However, no difference was noted in global radial strain between SSc patients and normal subjects. Of note, dSSc patients showed worse values of global longitudinal and circumferential strain as compared to lSSc patients.

Cardiopulmonary exercise testing

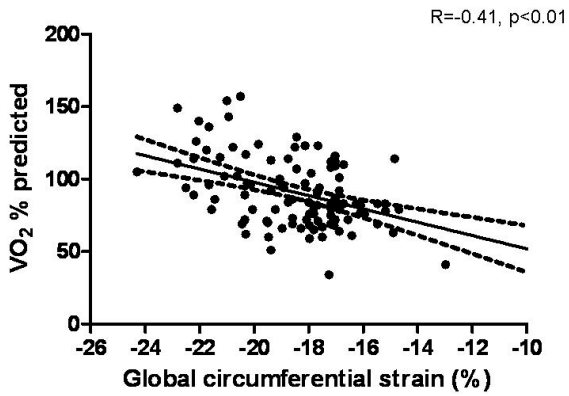
All SSc patients completed the CPET with at least 50W exercise level and reached anaerobic threshold; the heart rate recovery (HRR) was >12 beats/minute and the respiratory exchange ratio was >1.00, suggesting a satisfactory exercise capacity in the study population. The mean peak VO_2% predicted was 90.6±20.4% and the maximum exercise time was 9.9±3.6 min suggesting a relatively preserved functional capacity in the population. Patients with dSSc had a significantly lower peak VO_2% predicted compared to those with lSSc (83.2±21.1 vs. 99.7±24.7%, p<0.01).

According to Pearson's correlation analysis, peak VO_2% predicted was not related to conventional echocardiographic parameters including LV dimensions, LVEF and LV diastolic function (p>0.05). However, peak VO_2% predicted was significantly related to global longitudinal (r=-0.46, p<0.01), circumferential (r=-0.41, p<0.01) and radial (r=0.20, p=0.05) strains (Figure 3).

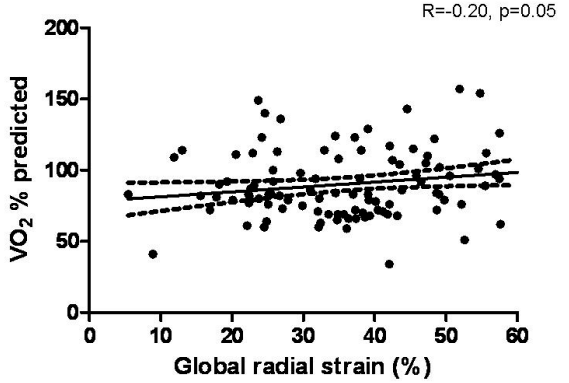
Univariate analysis revealed that among all the clinical and echocardiographic characteristics, age (β=0.24, Confidence interval [CI] = 0.09-0.83, p=0.02), subtype dSSc (β=0.40, CI = 0.30-0.79, p<0.01), underlying interstitial lung disease (β=0.24, CI = 2.23-20.6, p=0.02), TLC% predicted (β=0.40, CI = 0.30-0.79, p<0.01) and DLCO% predicted (β=0.49, CI = 0.46-0.96, p<0.01) were significantly associated with peak VO_2% predicted. Strain measurements were adjusted with the aforementioned parameters in a multivariate analysis, which demonstrated that global longitudinal (β=-0.36, CI = -0.21, -0.72, p<0.01) and circumferential (β=-0.34, CI = -0.19,-0.75, p<0.01) strains were independently associated with peak VO_2% predicted, together with age and DLCO%.



Panel A



Panel B



Panel C

Figure 3: Correlation between peak VO_2 % predicted and global longitudinal (Panel A), circumferential (Panel B) and radial (Panel C) strain measured by two-dimensional speckle tracking analysis. Dashed lines correspond to 95% confidence interval.

24-hour ECG Holter monitoring

Among the 100 SSc patients who underwent 24-hour ECG Holter monitoring, 28 (28%) patients had abnormal results. In particular, 9 patients presented with non-sustained ventricular tachycardia and 19 patients had ventricular ectopic >100 per day. No atrial arrhythmias were recorded.

Clinical and echocardiographic parameters differences between patients with or without abnormal Holter results are shown in Table 3. Patients with abnormal Holter results were more likely to be male and with underlying interstitial lung disease. Conventional LV systolic function, LV diastolic dysfunction grade, and S` velocity were similar between patients with or without abnormal Holter results. However, E/E` ratio was significantly higher in patients with abnormal Holter results. Moreover, global longitudinal and circumferential strains, but not global radial strain, were significantly impaired in patients with abnormal Holter results.

Univariate analysis demonstrated that the presence of abnormal Holter results was associated with male gender (OR = 2.94, CI = 1.12, 7.69, p<0.01), interstitial lung disease (OR = 3.32, CI = 1.32, 8.36, p<0.01), higher E/E` ratio (OR = 1.15, CI = 1.02, 1.32, p=0.04), and lower values of global longitudinal (OR = 1.71, CI = 1.24, 2.38, p<0.01) and circumferential strains (OR = 1.55, CI = 1.18, 2.03, p<0.01). After multivariate adjustment, both global longitudinal (OR = 1.47, CI = 1.05, 2.07, p=0.03) and circumferential (OR = 1.35, CI = 1.01, 1.82, p=0.04) strains remained the only independent predictors of abnormal Holter results in SSc patients.

Discussion

The results of the current study demonstrated that patients with SSc present subtle LV systolic dysfunction, as assessed by 2D speckle tracking strain analysis, despite normal LVEF and dimensions. More importantly, LV global longitudinal and circumferential strains, but not conventional echocardiographic parameters, were independently associated with functional capacity assessed by CPET, and ventricular arrhythmias detected by 24-hour ECG Holter monitoring.

Cardiac involvement in patients with SSc has been mainly described by the presence of elevated PASP and LV diastolic dysfunction.[5,6] Recent studies[5-7] using tissue Doppler imaging in relatively small groups of SSc patients, have also suggested an impairment in myocardial systolic deformation (strain), despite preserved LVEF and dimensions.[4,23] However, strain analysis by tissue Doppler imaging is significantly limited by angle dependency (the measure changes with the insonation angle) and does not allow for the evaluation of all LV segments and of different directions of myocardial deformation. The advent of 2D speckle tracking analysis overcomes these limitations and allows angle-independent, direct evaluation of LV global strain in all three orthogonal directions, providing more accurate assessment of LV function.[8]

Table 3: Clinical and echocardiographic characteristics of systemic sclerosis patients with and without abnormal 24 hour ECG Holter monitoring results.

	Normal Holter (n=72)	Abnormal Holter (n=28)	p value
Clinical characteristics			
Age, yrs	54±13	56±12	0.45
Female gender, n (%)	59(81.9)	17(60.7)	**0.04**
Interstitial lung disease, n (%)	9(32.1)	19(67.9)	**0.01**
Diffuse systemic sclerosis, n (%)	35(48.6)	19(67.9)	0.12
Modified Rodnan Skin Score	5.1±5.8	7.2±7.1	0.16
Immune markers:			
Anti-nuclear, n (%)	65(90.3)	26(92.9)	1.00
Anti-topoisomerase, n (%)	22(31.4)	13(46.4)	0.17
Anti-centromere, n (%)	17(26.2)	7(25)	1.00
Anti-RNP, n (%)	6(8.6)	1(3.6)	0.67
Lung function:			
FVC% predicted	89.0±17.8	83.2±18.5	0.17
TLC% predicted	64.6±17.2	60.4±16.1	0.25
DLCO% predicted	95.4±13.7	93.6±15.0	0.58
Conventional echocardiographic parameters			
LV end diastolic volume, ml	73.5±22.4	79.4±28.7	0.34
LV end systolic volume, ml	27.5±9.9	32.1±18.8	0.23
LV ejection fraction, %	63.9±6.6	62.8±9.1	0.57
PASP, mmHg	28.0±7.5	30.1±10.2	0.36
LV diastolic function, n (%)			
Normal	26 (36)	8 (29)	0.36
Mild	17 (24)	5 (18)	
Moderate	21 (29)	8 (29)	
Severe	8 (11)	7 (25)	
E` velocity, cm/s	8.6±2.9	8.1±2.6	0.35
E/E` ratio	9.4±3.8	11.7±4.0	**0.04**
S` velocity, cm/s	6.3±2.0	6.2±2.2	0.79
Speckle tracking analysis			
Global longitudinal strain, %	-18.5±1.5	-17.1±2.1	**<0.01**
Global circumferential strain, %	-18.7±2.0	-17.3±2.5	**0.01**
Global radial strain, %	37.8±14.0	33.7±13.1	0.17

Abbreviations: see Table 1 and 2.

The current study applied this novel analysis in a large cohort of SSc patients and found that both LV global longitudinal and circumferential strains were modestly but significantly impaired in SSc patients as compared to controls. The relatively small difference of strain values noted between the 2 groups could be explained by the fact that SSc patients in the present cohort were asymptomatic and had a relatively preserved functional capacity, suggestive of mild and subclinical cardiovascular involvement. Furthermore, dSSc patients showed worse values of global longitudinal and circumferential strains as compared to lSSc patients, confirming a more common and severe cardiac involvement in the diffuse form of the disease.[5, 24]

Therefore, the use of more sensitive echocardiographic parameters may enable the detection of subtle LV systolic dysfunction before clinical manifestation, not identified by conventional approaches. Of note, both the present result and the studies from Mele and Kepez et al[5,6] failed to show a significant difference in myocardial function by using tissue Doppler imaging derived S` velocity between SSc patients and controls. These findings therefore suggest that 2D speckle tracking derived strain analysis, which allows angle-independent and global LV functional assessment, is superior to tissue Doppler imaging derived S` velocity to detect subtle myocardial dysfunction in SSc patients.

Although the mechanism underlying LV systolic dysfunction is unknown, previous studies have demonstrated the presence of significant myocardial fibrosis in SSc patients, using delayed gadolinium enhanced magnetic resonance imaging.[25,26] These structural alterations, mainly caused by repeated focal ischemia due to abnormal vasoreactivity, may be responsible for myocardial dysfunction. Interestingly in the current study, multi-directional strain analysis demonstrated significant impairment of longitudinal and circumferential strains (shortening), but not of radial strain (thickening). This finding may suggest that myocardial involvement of the subendocardial layer (responsible for longitudinal and circumferential shortening) occurs earlier as compared to the subepicardial layer (responsible for radial deformation), since the subendocardium is more susceptible to ischemia and fibrosis phenomena. Nevertheless, the exact mechanism of myocardial dysfunction requires further studies.

Patients with SSc were shown to have reduced cardiopulmonary exercise capacity measured by VO_2% predicted, which could be caused by multiple factors.[27-30] Previous studies have suggested that lung pathology is one of the main determinants of impaired functional capacity in these patients.[28, 31] Similarly, the present study also showed the important role of lung function assessed by DLCO% predicted, which was independently associated with VO_2% predicted.[31] In addition, a recent study by Walkey and colleagues has also suggested that exercise induced LV diastolic dysfunction, undetected by resting echocardiography, was a cause of impaired exercise capacity.[29] However, the potential role of LV systolic dysfunction as an important contributing factor to functional capacity, has not been demonstrated before. Importantly, the present study demonstrated that

LV global longitudinal and circumferential strains were significantly related with VO_2% predicted, independently of age, SSc subtype and lung function. This observation thus provided direct evidence that LV systolic dysfunction significantly contributes to impaired functional capacity in patients with SSc. Therefore, novel 2D speckle tracking strain analysis may be used in conjunction with lung function testing in order to provide a global assessment and monitoring of the cardiopulmonary status in SSc patients.

Ventricular arrhythmias commonly occur in patients with SSc[32] and, are responsible for up to 6% of the deaths, as demonstrated by a recent study.[2] In particular, the presence of non-sustained ventricular tachycardias has been reported in 6-10% of patients with SSc and showed to be significantly associated with total mortality and sudden death.[31,32] In the current study, 24-hour ECG Holter monitoring was systematically performed in a large group of SSc patients and identified non-sustained ventricular tachycardias in 9% of the cases. Importantly at the multivariate analysis, LV systolic dysfunction, assessed by LV global longitudinal and circumferential strains, was the only independent predictor of ventricular arrhythmias (ventricular ectopics and non-sustained ventricular tachycardia). These results suggest that subtle LV systolic dysfunction is *per se* an important factor associated with ventricular arrhythmias and may also reflect the extent of myocardial fibrosis, which is a well-known arrhythmogenic substrate.[25] These novel echocardiographic parameters therefore represent a valuable tool to improve risk stratification of SSc patients. The current study underscores the need for implementing speckle tracking strain analysis in larger systemic sclerosis cohort studies, investigating risk stratification and potential protective effects of anti-arrhythmic strategies.

The current study was a cross-sectional analysis and therefore a causal relationship between impaired 2D speckle tracking derived strain and impaired functional capacity and ventricular arrhythmias in SSc patients could not be established. Moreover, the current population included SSc patients with preserved functional capacity and low prevalence of pulmonary hypertension and the results of the present study can not be extrapolated to SSc patients with severe cardiopulmonary involvement. Lastly, microvascular and macrovascular ischemia were not fully documented, since all patients had no clinical evidence of myocardial ischemia (neither during CPET) and invasive evaluations and/or vasoreactivity tests were therefore not performed. Future studies are required to evaluate the impact of both microvascular or macrovascular ischemia on 2D speckle tracking derived multi-directional strain in SSc patients.

In conclusion, patients with SSc are associated with LV systolic dysfunction measured by 2D speckle tracking strain analysis. Importantly, LV global longitudinal and circumferential strains independently predicted impaired functional capacity measured by CPET and ventricular arrhythmias detected by 24-hour ECG Holter monitoring. The use of this novel imaging technique may therefore improve risk stratification and monitoring of the cardiovascular involvement in patients with SSc.

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Reference List

(1) Bryan C, Knight C, Black CM, Silman AJ. Prediction of five-year survival following presentation with scleroderma: development of a simple model using three disease factors at first visit. *Arthritis Rheum* 1999;42:2660-5.

(2) Tyndall AJ, Bannert B, Vonk M et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis* 2010. 69:1809-15

(3) Follansbee WP, Miller TR, Cirtoss EI et al. A controlled clinicopathologic study of myocardial fibrosis in systemic sclerosis (scleroderma). *J Rheumatol* 1990;17:656-62.

(4) Allanore Y, Meune C, Vonk MC et al. Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of patients with systemic sclerosis. *Ann Rheum Dis* 2010;69:218-21.

(5) Mele D, Censi S, La Corte R et al. Abnormalities of left ventricular function in asymptomatic patients with systemic sclerosis using Doppler measures of myocardial strain. *J Am Soc Echocardiogr* 2008;21:1257-64.

(6) Kepez A, Akdogan A, Sade LE et al. Detection of subclinical cardiac involvement in systemic sclerosis by echocardiographic strain imaging. *Echocardiography* 2008;25:191-7.

(7) D'Andrea A, Stisi S, Bellissimo S et al. Early impairment of myocardial function in systemic sclerosis: Non-invasive assessment by Doppler myocardial and strain rate imaging. *Eur J Echocardiogr* 2005;6:407-18.

(8) Blessberger H, Binder T. Two dimensional speckle tracking echocardiography: basic principles. Heart 2010;96:716-22.

(9) Schuerwegh AJ, Schouffoer AA, Beaart-van deVoorde LJ, Tromp FJ, Ninaber MK, de Jong Z, Vliet Vlieland TP. Yearly, Standardized, comprehensive Assessment and Treatment Advice for Patients with Systemic Sclerosis (SSc): Feasibility of a Day Care Program. Arthritis Rheum 2009:60 (s10):1144.

(10) Schouffoer AA, Ninaber MK, Beaart-van de Voorde LJ, van der Giesen FJ, de Jong Z, Stolk J, Voskuyl AE, Scherptong RW, van Laar JC, Schuerwegh AJ, Huizinga TW, Vliet Vlieland TP. A randomised comparison of a multidisciplinary team care program with usual care in patients with systemic sclerosis. *Art Res Ther* 2011 (Epud ahead of print).

(11) Clements P, Lachenbruch P, Siebold J et al. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. *J Rheumatol* 1995;1281-5.

(12) LeRoy EC, Black C, Fleischmajer R et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988;15:202-5.

(13) Miller MR, Hankinson J, Brusasco V et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.

(14) Wanger J, Clausen JL, Coates A et al. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005;26:511-22.

(15) MacIntyre N, Crapo RO, Viegi G et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005;26:720-35.

(16) Lang RM, Bierig M, Devereux RB et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-63.

(17) Nagueh SF, Appleton CP, Gillebert TC et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;22:107-33.

(18) McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation* 2001;104:2797-802.

(19) Kircher BJ, Himelman RB, Schiller NB. Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. *Am J Cardiol* 1990;66:493-6.

(20) Delgado V, Ypenburg C, van Bommel RJ et al. Assessment of left ventricular dyssynchrony by speckle tracking strain imaging comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. *J Am Coll Cardiol* 2008;51:1944-52.

(21) ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *Am J Respir Crit Care Med* 2003;167:211-77.

(22) Smedema JP, Snoep G, van Kroonenburgh MP et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. *J Am Coll Cardiol* 2005;45:1683-90.

(23) de Groote P, Gressin V, Hachulla E et al. Evaluation of cardiac abnormalities by Doppler echocardiography in a large nationwide multicentric cohort of patients with systemic sclerosis. *Ann Rheum Dis* 2008;67:31-6.

(24) Follansbee WP, Curtiss EI, Medsger TA et al. Physiologic abnormalities of cardiac function in progressive systemic sclerosis with diffuse scleroderma. *N Engl J Med* 1984;310:142-8.

(25) Tzelepis GE, Kelekis NL, Plastiras SC et al. Pattern and distribution of myocardial fibrosis in systemic sclerosis: A delayed enhanced magnetic resonance imaging study. *Arthritis Rheum* 2007;56:3827-36.

(26) Hachulla AL, Launay D, Gaxotte V et al. Cardiac magnetic resonance imaging in systemic sclerosis: a cross-sectional observational study of 52 patients. *Ann Rheum Dis* 2009;68:1878-84.

(27) Sudduth CD, Strange C, Cook WR et al. Failure of the circulatory system limits exercise performance in patients with systemic sclerosis. *Am J Med* 1993;95:413-8.

(28) Alkotob ML, Soltani P, Sheatt MA et al. Reduced exercise capacity and stress-induced pulmonary hypertension in patients With scleroderma. *Chest* 2006;130:176-81.

(29) Walkey AJ, Ieong M, Alikhan M, Farber HW. Cardiopulmonary exercise testing with right-heart catheterization in patients with systemic sclerosis. *J Rheumatol* 2010;37:1871-7.

(30) Kovacs G, Maier R, Aberer E et al. Borderline pulmonary arterial pressure is associated with decreased exercise capacity in scleroderma. *Am J Respir Crit Care Med* 2009;180:881-6.

(31) Schwaiblmair M, Behr J, Fruhmann G. Cardiorespiratory responses to incremental exercise in patients with systemic sclerosis. *Chest* 1996;110:1520-5.

(32) John BK, James RS, Darya T et al. Prognostic importance of cardiac arrhythmias in systemic sclerosis. *Am J Med* 1988;84:1007-15.

CHAPTER 3

Impaired sexual function in female patients with Systemic Sclerosis: a cross-sectional study

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A. Schouffoer, J. van der Marel, P.T.M. Weijenborg, M.M. ter Kuile, A.Voskuyl, C.W. Vliet Vlieland, J.M. van Laar, T.P.M. Vliet Vlieland.

Abstract

Objective: To compare sexual function in female patients with systemic sclerosis (SSc) with healthy controls and to determine the association between disease characteristics and sexual function.

Methods: We conducted a cross-sectional study of 69 women with SSc (ages 18 to 60 years) and 58 age-matched controls. Assessment included the Female Sexual Function Index (FSFI), Female Sexual Distress Scale (FSDS), Hospital Anxiety and Depression Scale (HADS), Short Form 36 health survey, socio-demographic characteristics, and in patients only, the Health Assessment Questionnaire (HAQ).

Results: Of 69 eligible SSc patients 37 (54%) responded, in addition to 37 (64%) of 58 controls. The FSFI total score and the subscale scores for lubrication, orgasm, arousal and pain were significantly lower and FSDS scores were significantly higher in patients with SSc. Longer disease duration and higher levels of marital dissatisfaction were significantly related with low sexual function in patients with SSc. Longer disease duration, more depressive symptoms and the use of anti-depressants were significantly associated with sexual distress. Multivariate analyses indicated that marital distress was the only variable significantly associated with low sexual function in patients with SSc ($\beta = 0.40$, $P < 0.5$), whereas depression was the only variable significantly associated with sexual distress ($\beta = 0.32$, $P < 0.05$). The same pattern of associations was found in the healthy control group.

Conclusions: Women with SSc reported significantly impaired sexual functioning and more sexual distress then healthy controls. Impaired sexual functioning and sexual distress were associated with marital distress and depressive symptoms. These results indicate that in daily practice, inquiring after sexuality and screening for depression is indicated in every patient with SSc, irrespective of their clinical characteristics.

Introduction

Systemic sclerosis (SSc; scleroderma) is an autoimmune disease characterized by fibrosis of multiple organs. SSc was found to have a major impact on various aspects of life, including sexuality (1). In men with SSc, the prevalence of erectile dysfunction appears to be substantial (2). So far, the literature on sexual dysfunction in women with SSc is scarce.

Bhadauria et al. (3) compared sexual function between 60 patients with SSc and 23 women with rheumatoid arthritis (RA) or systemic lupus erythematosus matched for age and disease duration. It was found that women with SSc had a significantly lower number and intensity of orgasms and significantly more women with SSc reported skin tightness and heartburn, reflux or vomiting as symptoms causing problems during intercourse compared with control subjects. Sampaio-Barros et al (1) found that dyspareunie was mentioned by 49 (37%) of the 131 sexually active patients with SSc. All of these 49 patients reported vaginal dryness before, and worsening of symptoms after the onset of SSc. In a survey by Guerriere (4) 40% of 101 SSc patients reported to be sexually inactive, with only 7% attributing their sexual inactivity to SSc. None of these 3 studies had a study design with healthy controls. Moreover 2 of these studies did not use validated questionnaires to evaluate sexual complaints .

In both healthy subjects as well as patients with a chronic illness, including fibromyalgia, psychosocial factors such as relationship dissatisfaction and depression have been identified as determinants of impaired sexual function (5-8) . Recent studies confirm that the prevalence of depressive symptoms is high among patients with SSc, and a relation between depressive symptoms, disease severity and specific medical symptoms has been demonstrated (9,10).

Given the scarcity of data on sexual function among women with SSc, this study was designed to examine the type and extent of sexual problems in female SSc patients as compared to healthy women, and to determine associated variables of sexual function in this patient group. The aforementioned observations stress the need to take depression and relationship satisfaction into account.

Patients and methods

Study design

The study had a cross-sectional, multicenter design. Approval for this study was obtained from the Institutional Review Boards of two hospitals and a primary health care center. All participants gave written informed consent. They were compensated with 10 Euros ($12.71 US dollars) after returning the questionnaires.

Patients

Women with SSc were recruited at two academic rheumatology outpatient clinics between January 2007 and January 2008. Inclusion criteria were: diagnosis of SSc according to the American College of Rheumatology (formerly the American Rheumatism Association) criteria (11) and aged 18-60. The selection of patients was done by their treating rheumatologist.

Information leaflets, explaining the aim and the methods of the study, were either sent to all eligible patients by mail or handed over in person to all eligible patients. Patients were contacted by the principle investigator (AAS) two weeks later, unless the patient had already indicated to decline participation. All patients willing to participate were then sent a set of questionnaires. If the patient was invited by the rheumatologist during a visit at the outpatient clinic, and the patient was interested to participate, the set of questionnaires was provided immediately.

Healthy controls

Participating patients with SSc who were asked to invite a healthy female friend or family member of similar age (age range ± years) to participate in this study. Because the number of questionnaires returned by healthy relatives or friends was relatively low, a general practitioner (CWVV) invited another 25 women visiting a primary health care center, who had no SSc or other rheumatic disease and were ages 18-60,to participate in the study.

Assessment methods.

Sexual function and sexual distress

Sexual function was measured by the Female Sexual Function Index (FSFI), a 19-item self-report questionnaire that assesses sexual functioning in women in 6 separate subscales (desire, arousal, lubrication, orgasm, satisfaction, pain) (4,12,13). In addition, a total score (range 2-36) can be computed. A higher subscale or total score indicates better sexual function. A cut-off score of < 26.55 is proposed as a criterion for a sexual dysfunction (14). The Dutch version of the FSFI has good psychometric properties differentiates well between women with sexual dysfunctions and healthy controls (15). Sexual distress was measured with the Female Sexual Distress Scale (FSDS), which quantifies the personal distress that any sexual complaints cause (14). Consensus-based characterizations of female sexual dysfunction (FSD) have emphasized personal distress as an essential component of the definition of FSD. The total score ranges from 0-44, with higher scores representing more sexuality related personal distress. A cut off score of > 15 is proposed as a criterion for impaired sexual function (14). The Dutch version FSDS has good psychometric properties and is able to differentiate well between women with sexual dysfunctions and non-dysfunctional controls (15).

Quality of life

Quality of life was measured with the Short Form-36, which includes eight domain scores: physical functioning, role limitation due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitation due to emotional problems, and mental health. The scores of the SF-36 subscales range from 0-100, with higher scores indicating better quality of life. The subscales can be converted into two summary scales: the physical and mental component summary scale, standardized to a score with a mean ±SD of 50 ±10 in the general population. For that purpose, we used the scores from an age- and sex-matched, normative sample, drawn from a large, random, nationwide sample of adults (n=1742) from the general Dutch population (16) and factor score coefficients (17). The psychometric properties of this questionnaire have been found to be adequate (16;18).

Mental status

Anxiety and depression were measured by means of a Dutch version of the Hospital Anxiety and Depression Scale (HADS), a 14-item questionnaire (19,20). It was developed to indicate the possible presence of anxiety and depressive states in the setting of a medical outpatient clinic and is considered to be unbiased by coexisting general medical conditions (20,21). It contains two 7-items scales: one for anxiety and one for depression. Higher scores represent higher levels of anxiety and/or depression symptoms (range 0–21 per scale). The questionnaire is validated for the Dutch language and has good psychometric properties (20).

Disease characteristics and function

In patients with SSc, disease duration (years) and disease subset (limited or diffuse), were derived from the medical record. In addition, patients were asked to complete the Scleroderma Health Assessment Questionnaire (SHAQ), a 20-item questionnaire comprising 8 domains of activities of daily living with the final score ranging from 0 (no disability) to 3 (severe disability). It additionally contains scleroderma symptom visual analog scales (VAS) for Raynaud's disease, digital ulcers, intestinal symptoms, pulmonary symptoms, overall symptoms, and pain. All VAS were 100-mm horizontal lines, with the anchors on the left being no symptoms and no pain, whereas the anchors on. the right were the worst imaginable symptoms and severe pain (22). The SHAQ has been found to be a reliable outcome measure for disease severity in SSc (23).

Sociodemographic variables, menstrual status, marital satisfaction, abuse history, and medication usage. Sociodemographic variables included age, ethnic origin, status of living (living with a partner yes/no), paid employment (yes/no), and educational level (primary education [0–8 years], secondary education [9–16 years], or higher vocational education/university [17 years]). Patients were asked if they were still menstruating, and if not, for what reason (menopause, uterus extirpation, or hormonal therapy).

Sexual function may be influenced by drugs, such as antidepressants. Therefore, the questionnaire asked for information on current medication, which was afterward categorized by the principal investigator (AAS) using the following categories: analgesics, anti-inflammatory drugs, antidepressants, anxiolytics, and mood stabilizers. Marital dissatisfaction was measured by means of the subscale of general relationship dissatisfaction of the Maudsley Marital Questionnaire, a 20-item instrument measuring dissatisfaction with the subject's general relationship, sexual relationship, and life in general (24,25). Higher scores represent larger dissatisfaction. The questionnaire is validated for the Dutch language and has good psychometric properties (25).

To assess the prevalence of sexual and physical abuse during childhood and later years, the 7-item Sexual and Physical Abuse Questionnaire was used (26). Sexual abuse was restricted to sexual abuse with actual physical contact, and physical abuse was restricted to intentional violence resulting in some kind of physical injury.

Need for counseling. At the end of the questionnaires, participants were asked if they felt the need to talk to someone about sexual issues, and if so, who they would confide in: their partner, a friend, the general practitioner, the rheumatologist, a social worker, or someone else.

Statistical analysis

The calculation of the number of patients needed for this study was based on the difference between the FSFI total scores of patients with SSc and those of healthy controls. Assuming a FSFI total score of 30.5 in the healthy population and a difference of 5 points on the FSFI score to be clinically relevant, with alpha = 0.05 and beta =0.80, the number of patients (N) needed in each group to detect such a difference would be ($N= 7.85 \times (5.3)^2 \times 2 / (4.5)^2 \times 1$). All results were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort, case–control, and cross-sectional studies (27). Data entry was performed using Microsoft Office Access 2003 (Microsoft, Redmond, WA). Statistical analyses were executed using SPSS software, version 16.0 (SPSS, Chicago, IL).

P values (2-sided) less than 0.05 were considered statistically significant. Descriptive statistics were calculated for all variables. If appropriate, data sets were transformed to get a normal distribution. Univariate statistics were conducted in order to investigate whether patients with SSc differed on biographic, somatic, and psychological characteristics, sexual functioning, and sexual distress compared with healthy control subjects. In patients with SSc, the univariate association between sexual functioning and sexual distress with somatic and psychological characteristics was assessed with Pearson's, Spearman's, or point-biserial correlation coefficients as appropriate. Variables that were significantly correlated with sexual functioning or sexual distress were subsequently stepwise entered in a hierarchical multiple regression model.

Results

We invited 69 patients to participate in this study (Figure 1). Of these, 24 patients declined participation by returning the answering form or during the telephone contact with the principle investigator, because of embarrassment (n=5), no sexual relationship (n = 5), not being interested (n = 5), or for other/no reasons (n = 9). Of the 45 patients who were willing to participate, 37 returned the questionnaires, yielding a final response rate of 37 (54%) of 69. Of these, 33 patients volunteered to invite a relative or friend, resulting in 30 questionnaires returned by healthy controls. In addition, 7 of the 25 healthy women recruited at the primary health care center returned the questionnaire, yielding a final response rate of 37 (64%) of 58 healthy women. In 2 patients and 3 controls the SF-36 could not be calculated because of missing values (>10%). The general relation dissatisfaction subscale of the Maudsley Marital Questionnaire was not filled out by 6 of 37 patients and 1 of 37 control subjects because they were not involved in a long-term relationship. All other questionnaires had <5% missing values.

Differences in biographic, somatic and psychological characteristics between women with SSc and Controls

All SSc patients and healthy controls were Caucasian. There were no significant differences in characteristics between the patients and the healthy controls with respect to age, living status, education level, sexual or physical abuse history and menstrual status (Table 1). The mean age of SSc patients was 46 years and controls 43 years. A significantly smaller proportion of patients as compared to healthy controls had a paid profession. Moreover, the amount of working hours per week was significantly lower in those SSc patients having a paid profession than in healthy working women. There was no difference in the prevalence of sexual or physical abuse between SSc patients and controls. SSc patients did not differ from the healthy controls with respect to marital dissatisfaction. As for prescribed medication, significantly more SSc patients used anti-inflammatory drugs and antihypertensives as compared to healthy controls. There was no difference in proportions of patients and healthy controls using analgesics, anti-depressants, anxiolytics, oral anti-conceptives or hormonal replacement therapy. None of the patients or healthy control used antihistamines. There were no significant differences in any of the variables between patients with limited and patients with diffuse SSc (results not shown).

The results of the quality of life questionnaires and measures of mental and physical function are shown in Table 2. The mean SF-36 physical component summary subscale score was significantly lower in the patients with SSc than in the healthy controls. More specifically, the SF-36 subscales of role limitation due to physical problems ($P< 0.01$),

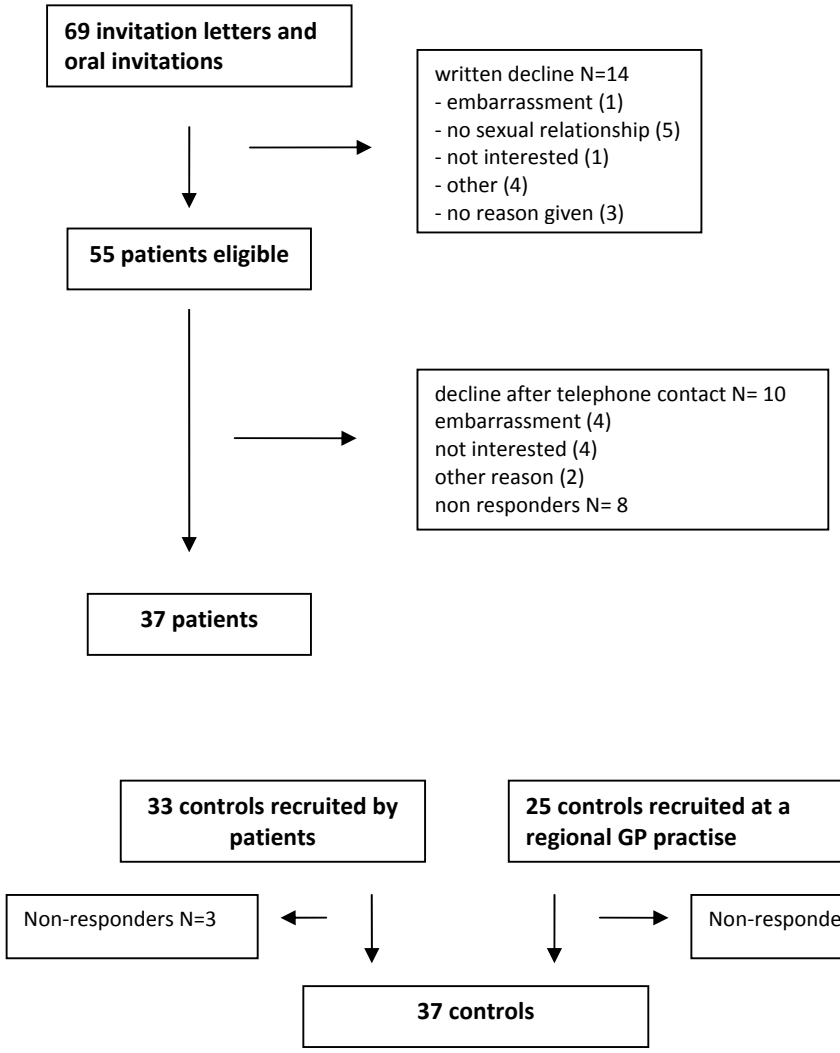

Figure 1: Flow chart of study participants. GP general practitioner

Table 1. Socio-demographic variables, menstrual status, medication and disease characteristics of SSc patients and healthy controls

	SSc Patients N=37	Healthy Controls, N=37	T or X2value#	P-value#
Age, years; M (SD)	45.6 (9.5)	43.3 (8.0)	-1.142	0.257
Living status; N (%)				
Partner (yes) N (%)	32 (86.5)	31 (83.8)	0.038	1.000
MMQ marital dissatisfaction M (SD)	14.4 (14.1)	14.2 (13.3)	-0.132	0.895
Education level; N (%) ¶				
low	8 (21.6)	10 (27.0)	-0.063	0.786
Medium	21 (56.8)	17 (45.9)	0.108	0.485
High	8 (21.6)	10 (27)	-0.063	0.786
Paid employment; N (%)	17 (45.9)	33 (89.2)	-0.462	0.000
Work hours/week; mean (SD)	19.9 (9.3)	22.6 (12.0)	0.797	0.429
Sexual abuse N (%)	7 (18.9)	13 (36.1)	-0.193	0.166
Physical abuse	5 (13.5)	4 (11.1)	0.037	1.000
Menopause (%)	10 (27.0)	6 (16.2)	0.131	0.397
Medication ♦ N (%)				
analgesics (incl. NSAID's)	10 (27.0)	5 (13.5)	2.105	0.147
anti-inflammatory drugs	13 (35.1)	4 (10.8)	6.237	0.013
anti-depressants,anxiolytics, moodstabilizers anti-	4 (10.8)	4 (10.8)	0	1.000
hypertensives (%)	24 (64.9)	1 (2.7)	32.415	0.000
OAC or HRT	3 (8.1)	7 (18.9)	1.858	0.173
Limited SSc; N (%)	18 (51.4)			
Diffuse SSc; N (%)	19 (48.6)			
Disease duration; M (SD)	6.5 (8.8)			

SSc = Systemic sclerosis; N= Number; M = mean; SD= Standard Deviation; MMQ= Maudsley Marital Questionnaire; ¶ Low: primary education (0-8 years), Medium: secondary education (9-16 years), High: higher vocational education/ university (17 years or more) ♦ NSAID; Non-Steroid Anti-Inflammatory Drug, OAC: oral anti-conceptives, HRT hormonal replacement therapy; # according to the t-test for independent sample or Chi-Square test

Table 2. Quality of life, mental functioning, physical and sexual functioning in SSc patients and healthy controls

	SSc Total group N=37	Healthy Controls N=37	t-value	P-value
Quality of life				
SF-36 (0-100); Mean (SD)				
physical component summary scale	36.4 (11.2)	56.3 (9.1)	-5.989	0.001
mental component summary scale	55.8 (8.4)	52.0 (6.4)	-1.632	0.103
Mental functioning				
HADS (0-21)				
anxiety; Mean (SD)	4.6 (2.9)	5.2 (3.4)	-0.500	0.617
depression; Mean (SD))	6.3 (2.2)	5.0 (1.8)	-2.529	0.011
Physical functioning				
HAQ Disability Score (0-3); Mean (SD)	0.88 (0.55)			n.a.
HAQ Visual Analog Scale Scores (0-100); Mean (SD)				
Raynaud's disease	51.8 (28.7)			n.a.
digital ulcers	18.6 (26.8)			n.a.
intestinal complaints	28.7 (30.5)			n.a.
pulmonal complaints	31.1 (25.2)			n.a.
overall complaints	46.7 (25.6)			n.a.
pain	41.5 (11.4)			n.a.
Sexual functioning				
FSFI subscales (0-6); Mean (SD)				
desire	3.1 (1.2)	3.4 (0.9)	-1.558	0.119
arousal	3.5 (1.9)	4.5 (1.2)	-2.836	0.005
lubrication	3.4 (2.1)	5.3 (1.1)	-4.418	0.000
orgasm	3.7 (2.2)	4.7 (1.4)	-2.360	0.018
satisfaction	4.0 (1.5)	4.6 (1.4)	-1.869	0.062
pain	3.0 (2.5)	5.0 (1.8)	-3.730	0.000
FSFI total (0-36) Mean (SD)	20.6 (9.4)	27.6 (6.2)	-3.779	0.000
FSDS (0-44) Mean (SD)	16.8 (12.4)	10.3 (10.9)	-2.415	0.016

SSc= Systemic Sclerosis, N= Number; M = mean; SD= Standard Deviation, SF = Shortform-36, HADS= Hospital Anxiety and Depression Scale, HAQ= Health Assessment Questionnaire FSFI= Female Sexual Function Score FSDS=Female Sexual Distress Score, n.a. not applicable; #=p-value of Mann-Whitney U test

general health perceptions ($P < 0.01$), and vitality ($P< 0.01$) denoted impairments in quality of life in the patients with SSc as compared with healthy controls (data not shown). Patients with SSc had significantly higher HADS depression subscale scores than healthy controls. Except for significantly higher mean VAS scores for Raynaud's phenomenon in the limited SSc group than in the diffuse SSc group, there were no statistically significant differences between the 2 types of SSc for any of the clinical variables (results not shown).

Differences in sexual function and sexual distress between women with SSc and controls. The FSFI total score and all subscale scores (except for the subscales desire and satisfaction) were significantly lower in the SSc group than in the healthy controls (Table 2). In addition, FSDS scores were significantly higher in patients with SSc than in the healthy controls. FSFI total scores, subscales, and FSDS scores did not differ between limited and diffuse patients with SSc (data not shown). With the application of the cut off score of 26.55, 26 (70%) of 37 patients would be considered to have an impaired sexual function, whereas with the FSDS cut off score of 15, 21 (57%) of 37 patients would be considered to have increased sexual distress. According to these cut off values, 18 (47%) of the 37 patients would be considered to have sexual dysfunction (defined as both impaired sexual function plus high levels of sexual distress).

Univariate predictors of sexual functioning. Among patients, marital dissatisfaction and disease duration were significantly associated with the FSFI total score, with participants with more marital dissatisfaction and longer disease duration showing more impaired sexual function (Table 3). The usage of antidepressants, more depressive symptoms, and longer disease duration were statistically significantly associated with more sexual distress.

In the hierarchical multiple linear regression models, only marital distress (β=-0.40, t= 2.32, $P< 0.05$) was significantly associated with the FSFI total score and it explained 16% of the variance in the FSFI total score. Disease duration did not account for a significantly additional proportion of variance in the FSFI total score ($P > 0.90$). For the dependent variable FSDS score, after controlling for the use of antidepressants (β= 0.31, t = 1.97, P=0.057), depression (β= 0.32, t= 2.05, $P< 0.05$) was entered into the equation, explaining an additional proportion of 10% of the variance in sexual distress (F[1,33] =4.2, $P< 0.05$). Disease duration did not account for a significant additional proportion of variance in the FSDS score ($P> 0.70$).

Repetition of these analyses in the healthy women yielded a similar pattern: higher levels of marital distress were significantly associated with more sexual problems and higher levels of depressive symptoms were significantly associated with higher levels of sexual distress (data not shown).

Table 3. Pearson correlation coefficients of FSFI total score and FSDS with socio-demographic variables, menstrual status, medication, quality of life, physical and mental functioning and disease characteristics for patients

	FSFI SSc N=37	FSDS SSc n=37
Age	0.14	-0.22
Partner	0.07	0.10
MMQ relation satisfaction	0.40*	0
Education level (low-medium-high)	-0.10	0.09
Paid employment	0.12	-0.12
Sexual abuse	-0.04	0.15
Physical abuse	-0.08	0.03
Menopause	0.22	-0.16
Medication:		
analgesics (incl. NSAID's)	-0.12	-0.03
anti-inflammatory drugs	-0.13	-0.22
anti-depressants, anxiolytics, mood stabilizers	0.27*	0.28*
antihypertensives	0.04	-0.11
OAC or HRT	0.06	0.14
SF-36		
physical component summary scale	0	-0.23
mental component summary scale	0.08	0.29*
HADS		
anxiety	0	0.23
depression	0.08	0.33*
Disease subset diffuse	-0.07	0.12
Disease duration	0.33*	0.35*
HAQ	0.07	0.20
HAQ Visual Analog Scale Scores		
Raynaud's disease	-0.02	0.15
digital ulcers	-0.05	0.16
intestinal complaints	-0.01	0.16
pulmonal complaints	-0.06	0.17
overall complaints	-0.11	0.29
pain	0	0.18

*= p<0.05, NSAID; Non-Steroid Anti-Inflammatory Drug, OAC: oral anti-conceptives, HRT hormonal replacement therapy, SF = Shortform-36, HADS= Hospital Anxiety and Depression Scale, HAQ= Health Assessment Questionnaire FSFI= Female Sexual Function Score FSDS=Female Sexual Distress Score

Need for counselling. Six (16%) of the SSc patients reported a need to talk to someone about current sexual problems, none of the patients mentioned their rheumatologist as a care provider in whom they would confide, only 1 mentioned their General Practitioner

Discussion

In this cross-sectional study it was found that sexual function was significantly impaired and more sexual distress was reported in women with SSc as compared with healthy controls. None of the specific disease characteristics of SSc were found to be associated with sexual problems or sexual distress in patients with SSc. Marital dissatisfaction was significantly associated with impaired sexual function, whereas depression was the only clinical variable that was associated with sexual distress.

Considering the large variety of SSc-related impairments and limitations that could affect sexual functioning, the lack of studies on this subject is remarkable. There are multiple effects of SSc on the skin and musculoskeletal systems that could have an impact on sexual functioning, including skin thickening resulting in decreased sensibility, decreased hand function, pain, and contractures; Raynaud's phenomena; digital ulcers; and muscle atrophy (28,29). Vaginal dryness and decreased lubrication may lead to dyspareunia (3). Vaginal ulcers and skin inflammation can result in fibrotic narrowing of the introitus (30). Fatigue and chronic pain may also influence sexual activity, as was demonstrated in patients with RA and chronic noncancer pain due to other musculoskeletal illness (31,32). Moreover, the physical consequences of the disease may have a negative effect on self-esteem and/or lead to depression and anxiety, which have been found to significantly affect sexual functioning in women (33–35).

In our study, a significant impairment of sexual functioning in women with SSc as compared with healthy women was seen. Our findings are difficult to compare directly with the currently available studies on sexual function in women with SSc due to differences in study design and outcome measures. The FSFI was used in only 1 study in patients with SSc, and an impairment of the FSFI in all domains, including desire and satisfaction, was observed (4). However, because only an abstract is available, no further information on the extent of the reduction is available. Similar to the results of our study, lubrication and frequency and intensity of orgasms were also found to be impaired by Bhadauria et al (3), whereas pain was also identified as a problem in the study by Sampaio-Barrros et al (1). However, the degree to which these complaints occurred cannot be compared with our data, because in these studies self-provided questionnaires were used. Bhadauria et al (3) reported a decrease of desire for intercourse in 57% of 60 women with SSc, but participants were not asked about sexual behaviours other than intercourse. In contrast, in our study desire and satisfaction were not impaired. In none of these studies was a comparison with controls made.

Sexually related personal distress, which is considered an important feature of sexual dysfunction (14), was never evaluated in SSc. In our study, an evident increase as compared with controls was seen. In a population-based sample of middle-aged Australian women (7), 34 (21%) of 166 participants with sexual problems showed increased distress.

In a population-based sample of heterosexual American women ages 18–60 years, it was found that sexual problems were associated with distress about the relationship (36). Furthermore, sexual distress was related to both emotional well-being and the emotional relationship with the partner. These associations were partly also demonstrated by our data. Furthermore, no disease-specific variable was found to be associated with sexual functioning or sexual distress in our study. We can conclude that sexual functioning and sexual distress in women with SSc are more strongly associated with psychological characteristics and to a lesser degree with disease-specific characteristics. Considering the cross-sectional design, the findings of our study have to be interpreted with caution, because the correlational nature of the findings regarding SSc, sexual functioning, depression, and marital distress precludes conclusions concerning the causality of relationships between these variables.

Patients with limited SSc reported as many problems with sexual function as patients with diffuse disease. This finding is in accordance with the outcomes of Guerriere et al (4), who found that FSFI scores were unrelated to disease classification. Moreover, in both that study and the present research, no relationship between disease severity and sexual function was found, whereas depressive symptoms were. This would imply that in daily clinical practice, attention should be paid to sexual functioning in all women with SSc, irrespective of the subtype and severity of the disease, and attention should be paid to possible depressive symptoms.

Health care professionals, however, tend to neglect patients sexual health; often they find it difficult to address sexual issues. In a study performed in a medical and nursing staff of a nephrology department, 86% of the professionals admitted not giving sufficient attention to and 92% admitted never initiating discussion about sexual issues with patients (37). In a questionnaire survey on views of multidisciplinary health professionals about discussing sexual issues with patients, most respondents (90%) agreed that addressing sexual issues ought to be part of the holistic care of patients (38). However, most staff (86%) was found to be poorly trained and most (94%) were unlikely to discuss sexual issues with their patients. This suggests that training in sexuality and sexual issues should be implemented as part of the training of health care professionals. In a study on the effects of RA on sexual activity, 37 patients (66%) had never been asked by any health professional about the impact of their disease on their sexuality, and 29 (59%) of 49 said they would not talk to someone if they had a problem (32). Our results showed that only 6 (16%) of the 37 patients with SSc felt the need to talk with someone about their sexual problems, and if they did want

to talk to someone, they preferred someone who was not a health professional. The impact of illness on sexuality thus seems to be a problem that both patients and health professionals find hard to discuss.

Some patients with SSc may have found their own way of coping with sexual problems. Still, patients may benefit from treatment or guidance by their rheumatologist or rheumatology nurse. Saad and Behrendt stated that an open discussion with patients with SSc on their concerns about sexuality, promoting communication between partners and proper information, is essential in patient care (39).

Specific suggestions in order to enhance comfort during sexual activity are usage of lubricants, providing a warm environment, avoiding meals and elevating the bed prior to sexual activity, and re-evaluating medical therapy if needed. Although alleviation of problems thus can be achieved, a holistic approach to impaired sexual function in patients with SSc is highly recommended. Referral to a gynaecology department should be considered, because a thorough physical examination may provide essential information.

This study had a number of limitations. First, selection bias in the group of patients as well as the controls cannot be excluded. We could not make a comparison of those who refused participation because we did not gather information on the characteristics of the patients who declined participation or did not respond. Moreover, despite the fact that the response rates were comparable with those in other studies on sexual functioning, the sample sizes of patients and healthy controls were relatively small. Second, it would have been helpful to know the exact reasons for sexual inactivity in patients and controls. Unfortunately, no information was obtained about the length of the relationships between the patients and their partners, so the influence of the length of the relationship on sexual function could thus not be evaluated. Finally, we failed to ask our participants whether a rheumatologist had ever inquired about sexual problems. This would have been illustrative in demonstrating how often the subject was raised in an outpatient clinic setting. Despite these limitations, this study may contribute to a better understanding of the impact of SSc on well-being, as it is the first study to our knowledge to compare sexual function in patients with SSc with that of healthy controls. Moreover, no study to date has used multiple validated measures to evaluate sexual function in SSc.

In conclusion, impaired sexual function and more sexual distress are found in patients with SSc compared with healthy controls. Although our patients are reticent about discussing sexual problems with their rheumatologist, the subject should not be avoided during consultation. Inquiry about sexuality and offering the opportunity to identify problems will improve the quality of patient care. Patients may benefit from referral to proper counselling once sexual problems are openly discussed.

Literature

1. Sampaio-Barros PD, Samara AM, Marques Neto JF. Gynaecologic history in systemic sclerosis. Clin Rheumatol 2000;19: 184–7.
2. Hong P, 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;31:508–13.
3. Bhadauria S, Moser DK, Clements PJ, Singh RR, Lachenbruch PA, Pitkin RM, et al. Genital tract abnormalities and female sexual function impairment in systemic sclerosis. Am J Obstet Gynecol 1995;172:580–7.
4. Guerriere JA, Rosen RC, Seibold JR. Quality of life and sexual function in women with systemic sclerosis (SSc) [abstract]. Arthritis Rheum 2001;44 Suppl:S328.
5. Kocak M, Basar MM, Vahapoglu G, Mert HC, Gungor S. The effect of Behc¸et's disease on sexual function and psychiatric status of premenopausal women. J Sex Med 2009;6:1341–8.
6. Enzlin P, Mathieu C, van den BA, Bosteels J, Vanderschueren D, Demyttenaere K. Sexual dysfunction in women with type 1 diabetes: a controlled study. Diabetes Care 2002;25:672–7.
7. Dennerstein L, Guthrie JR, Hayes RD, Derogatis LR, Lehert P. Sexual function, dysfunction, and sexual distress in a prospective, population-based sample of mid-aged, Australian born women. J Sex Med 2008;5:2291–9.
8. Kalichman L. Association between fibromyalgia and sexual dysfunction in women. Clin Rheumatol 2009;28:365–9.
9. Thombs BD, Hudson M, Taillefer SS, Baron M, and the Canadian Scleroderma Research Group. Prevalence and clinical correlates of symptoms of depression in patients with systemic sclerosis. Arthritis Rheum 2008;59:504–9.
10. Thombs BD, Taillefer SS, Hudson M, Baron M. Depression in patients with systemic sclerosis: a systematic review of the evidence. Arthritis Rheum 2007;57:1089–97.
11. Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.
12. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26:191–208.
13. Rosen RC. Assessment of female sexual dysfunction: review of validated methods. Fertil Steril 2002;77 Suppl 4:S89–93.
14. Derogatis LR, Rosen R, Leiblum S, Burnett A, Heiman J. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. J Sex Marital Ther 2002;28:317–30.
15. Ter Kuile MM, Brauer M, Laan E. The Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS): psychometric properties within a Dutch population. J Sex Marital Ther 2006;32:289–304.
16. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055–68.
17. Ware JE, Kosinski M, Keller SD. SF-36 health survey manual and interpretation guide. Boston: The Health Institute; 1994.

18. Essink-Bot ML, Krabbe PF, Bonsel GJ, Aaronson NK. An empirical comparison of four generic health status measures: the Nottingham Health Profile, the Medical Outcomes Study 36-item Short-Form Health Survey, the COOP/WONCA charts, and the EuroQol instrument. Med Care 1997;35:522–37.
19. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361–70.
20. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27:363–70.
21. Petersen RW, Ung K, Holland C, Quinlivan JA. The impact of molar pregnancy on psychological symptomatology, sexual function, and quality of life. Gynecol Oncol 2005;97:535–42.
22. Clements PJ, Wong WK, Hurwitz EL, Furst DE, Mayes M, White B, et al. The Disability Index of the Health Assessment Questionnaire is a predictor and correlate of outcome in the high-dose versus low-dose penicillamine in systemic sclerosis trial. Arthritis Rheum 2001;44:653–61.
23. Merkel PA, Herlyn K, Martin RW, Anderson JJ, Mayes MD, Bell P, et al, for the Scleroderma Clinical Trials Consortium. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. Arthritis Rheum 2002;46:2410–20.
24. Crowe MJ. Conjoint marital therapy: a controlled outcome study. Psychol Med 1978;8:623–36.
25. Arrindell WA, Boelens W, Lambert H. On the psychometric properties of the Maudsley Marital Questionnaire (MMQ): evaluation of self-ratings in distressed and normal volunteer couples based on the Dutch Version. Pers Individ Dif 1983;4: 293–306.
26. Kooiman CG, Ouwehand AW, ter Kuile MM. The Sexual and Physical Abuse Questionnaire (SPAQ): a screening instrument for adults to assess past and current experiences of abuse. Child Abuse Negl 2002;26:939–53.
27. Von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–9.
28. Medsger TA, Jr. 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: 255–73, vi.
29. Paquette DL, Falanga V. Cutaneous concerns of scleroderma patients. J Dermatol 2003;30:438–43.
30. Wilson D, Goerzen J, Fritzler MJ. Treatment of sexual dysfunction in a patient with systemic sclerosis. J Rheumatol 1993;20:1446–7.
31. Kwan KS, Roberts LJ, Swalm DM. Sexual dysfunction and chronic pain: the role of psychological variables and impact on quality of life. Eur J Pain 2005;9:643–52.
32. Hill J, Bird H, Thorpe R. Effects of rheumatoid arthritis on sexual activity and relationships. Rheumatology (Oxford) 2003;42:280–6.
33. Haythornthwaite JA, Heinberg LJ, McGuire L. Psychologic factors in scleroderma. Rheum Dis Clin North Am 2003;29: 427–39.
34. Legendre C, Allanore Y, Ferrand I, Kahan A. Evaluation of depression and anxiety in patients with systemic sclerosis. Joint Bone Spine 2005;72:408–11.
35. Angst J. Sexual problems in healthy and depressed persons. Int Clin Psychopharmacol 1998;13 Suppl 6:S1–4.

36. Bancroft J, Loftus J, Long JS. Distress about sex: a national survey of women in heterosexual relationships. Arch Sex Behav 2003;32:193–208.
37. Ho TM, Fernandez M. Patient's sexual health: do we care enough? J Ren Care 2006;32:183–6.
38. Haboubi NH, Lincoln N. Views of health professionals on discussing sexual issues with patients. Disabil Rehabil 2003; 25:291–6.
39. Saad S, Behrendt A. Scleroderma and sexuality. J Sex Res 1995;33:215–20.

Sexual function in women with systemic sclerosis: Comment on the article by Schouffoer et al.

Arthritis Care Res (Hoboken). 2010 Aug;62(8):1200

Knafo R, Jewett LR, Bassel M, Thombs BD.

In an article published recently in *Arthritis Care & Research*, Schouffoer et al reported that women with systemic sclerosis (SSc; scleroderma) have greater sexual impairment and distress than healthy controls, and the authors recommended that health care professionals inquire about sexuality with all SSc patients (1). Two previous studies reported similarly that women with SSc have greater sexual impairment than women in the general population (2) or compared with women with other medical diseases where sexual problems are more routinely addressed (3). The broad recommendation of Schouffoer et al for routine inquiry about sexual problems, however, appears to be premature. Only 16% of patients in the study by Schouffoer et al expressed a desire to discuss sexual problems, and none wished to do this with their rheumatologist.

While there is a great need to better address sexuality in SSc, it is important to demonstrate the patient benefits of routine inquiry before a specific recommendation is made. A call for routine inquiry about sexuality should only be made once we have provided a way of doing this that is agreeable to patients, feasibly implemented by physicians, and linked to an effective intervention and patient benefit (4). In order to develop and test an intervention, it is also important that we understand which disease and psychosocial characteristics may lead to sexual dysfunction. Schouffoer et al reported that "none of the specific disease characteristics of SSc were found to be associated with sexual problems" (1). Previous studies, however, have found that women with diffuse SSc have significantly greater impairment than those with limited SSc (3) and that women with SSc are more likely to experience dyspareunia, vaginal dryness, and vaginal ulcerations/fissures than women with other rheumatic diseases (5). The study by Schouffoer et al did not include an assessment of key SSc variables that may be related to impaired sexual function.

Furthermore, based on the study's small sample size, there was only 32% power to detect a moderate difference in sexual impairment between limited and diffuse patients (e.g., _ _ 0.50). Studies are needed that investigate multiple predictors of sexual impairment, including both physical symptoms of SSc and psychological factors, with sufficient power to detect potential upstream factors. The study by Schouffoer and colleagues is a step in the right direction and contributes to the limited body of researchon sexual function in SSc. However, more research is needed before broad recommendations to routinely inquire quire about sexuality can be made. Before we ask health providers to reach beyond their level of comfort and training

to address sexual issues, we need to provide them with a way to do it effectively. In the interim, patients may benefit from a referral to a specialist, as Schouffoer et al suggest, or from the provision of information (e.g., in the form of a pamphlet) about common SSc sexual issues, which may normalize the subject and facilitate discussion with a health professional (3).

1. Schouffoer AA, van der Marel J, ter Kuile MM, Weijenborg PT, Voskuyl A, Vliet Vlieland CW, et al. Impaired sexual function in women with systemic sclerosis: a cross-sectional study. Arthritis Rheum 2009;61;1601–8.
2. Impens AJ, Rothman J, Schiopu E, Cole JC, Dang J, Gendrano N, et al. Sexual activity and functioning in female scleroderma patients. Clin Exp Rheumatol 2009;27 Suppl 54:S38–43.
3. Knafo R, Thombs BD, Jewett LR, Hudson M, Wigley F, Haythornthwaite J. (Not) talking about sex: a systematic comparison of sexual impairment in women with systemic sclerosis and other chronic disease samples. Rheumatology (Oxford) 2009;48:1300–3.
4. Raffle AE, Gray JA. Screening: evidence and practice. Oxford (UK): Oxford University; 2007.
5. Saad SC, Pietrzykowski JE, Lewis SS, Stepien AM, Latham VA, Messick S, et al. Vaginal lubrication in women with scleroderma and Sjogren's syndrome. Sex Disabil 1999;17:103–13.

Reply

A. Schouffoer, MD, M.M. ter Kuile, PhD, T.P.M. Vliet Vlieland, MD, PhD

We thank dr Knafo and colleagues for their commentary on our study, and the summary of recent publications that further illustrate the negative impact that Systemic Sclerosis may have on sexual function in female patients. Several specifically scleroderma-related problems were recently identified by Impens (1) as contributing factors to sexual difficulties, with fatigue, bodily pain, vaginal dryness and discomfort being most frequently mentioned by 101 female systemic sclerosis patients. We agree with the recommendation that more research is needed in order to identify predictors of sexual impairment. Indeed, the lack of correlation between levels of sexual functioning and disease classification in our study may be due to the small sample size. However, in the larger study by Impens also no correlation was found.

Considering the growing evidence as previously discussed, we feel that a health professional's simple question 'are problems in sexual functioning present?' will be acceptable for most patients. Moreover, considering the frequently mentioned scleroderma specific complaints (1) it is very likely that a considerable number of female patients may benefit from simple health interventions (vaginal lubricants; medication advice, relaxation techniques and energy conservation), either provided by their rheumatologist, or other consulted health professional.

In other chronic impairment it has been recognized that dealing with sexual problems should be addressed in medical rehabilitation (2, 3), although reluctance of both patients as well as health professionals to discuss sexuality is known. The low percentage of 16% of our patients indicating a need to talk about possible sexual problems cannot not easily be explained, and demonstrates the need for further studies. First, the reported proportion pertains to the whole group we studied, and not to the subgroup of patients with sexual impairments. Moreover there is research illustrating that patients expect sexual issues to be brought up by the health professional and not by themselves (4). Although patient mere education by pamphlets (as advocated by Knafo et al) contributes to open communication, it also leaves the initiative with the patient with a risk of avoidance of the subject. We agree with Knafo and colleagues that an important condition for discussing matters of sexuality is a health professional that is comfortable with the subject. In a large British survey it was found that doctors discussed sexual issues significantly more often than other health professionals (N = 813) (5). The self rated sexological competence (rate 0-10, 10 being excellent) of 42 physicians in the Netherlands (6) was found to be less then sufficient before training (mean 5.8 (SD 1.1) and sufficient after a training (mean 6.7 (SD 1.2), illustrating the need for improvement of competences.

1. Impens AJ, Rothman J, Schiopu E, Cole JC, Dang J, Gendrano N, et al. Sexual activity and functioning in female scleroderma patients. Clin Exp Rheumatol 2009;27 (Suppl. 54):S38-S43.
2. McLaughlin, J., Cregan, A.: Sexuality in stroke care: a neglected quality of life issue in stroke rehabilitation? A pilot study. Sex. Disabil. 23, 213–226 (2005)
3. Eisenberg, M.G., Rustad, L.C.: Sex education and counseling program on a spinal cord injury service. Arch. Phys. Med. Rehabil. 57, 135–140 (1976)
4. Leibowitz, R.Q.: Sexual rehabilitation services after spinal cord injury: what do women want? Sex. Disabil. 23, 81–107 (2005)
5. Haboubi, N.H., Lincoln, N.: Views of health professionals on discussing sexual issues with patients. Disabil. Rehabil. 25, 291–296 (2003)
6. Gianotten, W.L., Bender, J.L., Post, M.W.M., Ho¨ing, M.: Training in sexology for medical and paramedical professionals: a model for the rehabilitation setting. Sex. Relat. Ther. 21, 303–317 (2006)

CHAPTER 4

Translation, cross-cultural adaptation and validation of the Mouth Handicap in Systemic Sclerosis questionnaire (MHISS) into the Dutch language

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A.A. Schouffoer, E. Strijbos, A.J.M. Schuerwegh, L Mouthon, T.P.M. Vliet Vlieland.

Abstract

Background and Objective: The Mouth Handicap in Systemic Sclerosis (MHISS) is a French-generic questionnaire evaluating mouth-opening restriction, dryness and aesthetic concerns. The aim of this study was to translate and adapt the MHISS questionnaire into the Dutch language and evaluate its psychometric properties.

Methods: The MHISS was translated according to international guidelines, field-tested among 16 systemic sclerosis (SSc) patients and adapted. Subsequently, the Dutch MHISS was administered to 52 SSc-patients visiting the outpatient or daypatient clinic of a university hospital, and re-administered after 2 weeks. Internal consistency was tested by computing Cronbach's alpha. Test-retest reliability was determined by computing the intraclass-correlation coefficient (ICC), and validity by determining associations with measures of overall functioning (Health Assessment Questionnaire; HAQ), maximum mouth opening (MMO; mm), subjective xerostomia (Visual Analog Scale; VAS) and objective xerostomia (Saxon test).

Results: Patients had mean ± standard deviation (SD) age and disease duration of 55±21 and 7.2±7.3 years. Twenty-seven (52%) patients had diffuse cutaneous SSc. The mean Dutch MHISS score was 17.5 (SD 10.0) with Cronbach's alpha being 0.862. Dutch MHISS scores differed significantly between patients with high and low disability levels (HAQ, MMO, and subjective and objective xerostomia divided according to the median; paired t-test). Spearman Rank correlations with HAQ (r=0.599, p=0.000), MMO (r=-0.518, p=0.000) and subjective xerostomia (r=0.536, p=0.000) were moderate, correlation with objective xerostomia did not reach statistical significance. The ICC was 0.94.

Conclusion: The Dutch version of the MHISS demonstrated good psychometric properties and is useful in assessing mouth disability in SSc-patients.

Introduction

Scleroderma or systemic sclerosis (SSc) is an auto-immune disease with skin fibrosis, involvement of multiple organs and impaired physical and mental functioning (1).Two major subtypes are distinguished, limited and diffuse cutaneous SSc. The face and mouth are frequently affected, resulting in nasal ala atrophy, a beaked nose, diminished expression and a diminished mouth opening. This may impair articulation, food intake, oral hygiene and result into difficulties for dental treatment (2-4). Mouth dryness is frequently present (5-7) and may further compromise dental health.

Adequate identification and evaluation of limitations in mouth functioning in SSc patients by means of a specific measurement instrument is mandatory, as symptoms can be alleviated by treatments such as artificial saliva, advices on diet and oral hygiene, mouth opening exercises or intensive dental care, thus improving patient care (8,9).

For this reason, Mouthon et al. presented the Mouth Handicap In Systemic Sclerosis (MHISS) questionnaire in 2007. The MHISS is a short, easy to fill out questionnaire evaluating the degree of mouth disability in patients with SSc according three domains: mouth opening restriction, mouth dryness and aesthetic concerns (10). The MHISS score explained up to 36.5% of the variance of the Health Assessment Questionnaire (HAQ) in a study including 71 SSc patients (8). The MHISS was developed in French, and validated in French and Italian (10;11).

Given the necessity to identify and evaluate mouth handicap in Dutch patients with SSc, the objective of this study was to translate and adapt the MHISS into a Dutch language version and evaluate its internal consistency, reliability and validity.

Patients and methods

Study design

This study had a cross-sectional design. It was executed at the outpatient and day patient clinics of the Department of Rheumatology of the Leiden University Medical Center between April 2009 and June 2009. The assessments were done once, except for the MHISS which was administered twice with an interval of two weeks. Ethical approval was obtained from the Institutional Review Board of the Leiden University Medical Center.

Translation and adaptation of the MHISS

The MHISS (see Appendix) consists of 12 items, with the score representing the frequency of the presence of symptoms or complaints: 0 (never), 1 (rarely), 2 (occasionally), 3 (often) and 4 (always). Three domains are characterized: (a) mouth opening; items 1,3,4,5 and 6; (b) mouth dryness; items 2,7,8,9 and 10; (c) aesthetic concerns; items 11 and 12. The total scale score ranges from 0 to 48, with higher scores indicating more mouth functional limitations.

The MHISS was translated and adapted according to the international guidelines for cross-cultural adaptation of health-related quality of life measures (12;13). First, two bilingual, native Dutch speaking translators of whom one was medically educated and one was a lay person translated the MHISS from French into Dutch. The two translations were compared and combined into one draft version in Dutch. Secondly, this draft Dutch version was translated in French by two native French speaking translators, again one medically educated, one a lay person. Thirdly, an expert panel consisting of a methodologist (TPMV) and two rheumatologists (AAS, AJS) evaluated the final version of the questionnaire regarding grammatical issues, cultural relevance and content validity for the Dutch population. According to the review of the expert panel, no significant modifications needed to be made.

The final version was field-tested among 16 SSc patients from the outpatient clinic of the Leiden University Medical Center (mean age 51.8 years, SD 12.4; mean disease duration 7.9 years, SD 6.7; six patients (40%) had diffuse SSc). They were asked to record the time it took to fill out the questionnaire and to give a written comment to each item of the Dutch MHISS if they felt the question was inappropriate, difficult to answer or not fully understood. Respondents were also asked if they felt that any important issues had been omitted. Patients could clarify their comments in a telephone interview that followed within one week after handing out the questionnaire. The comments and suggestions were subsequently discussed with the developer (LM).

The median time needed to fill in the questionnaire was 10 min (interquartile range 2-30 min). No comment was made regarding lay-out. Two patients felt questions 7 and 8 showed overlap, none of the questions were considered contradictive. The other comments in the field test resulted in two major changes in the Dutch MHISS:

(a) Three patients had dentures, two of them felt they were not able to answer items 4 and 5 concerning 'dental health' and requested an extra score option 'not applicable". Subsequently for items 4 and 5 apart from the options 0 (never), 1 (rarely), 2 (occasionally), 3 (often) and 4 (always), the option not applicable because of dentures was added. In case of a 'not applicable' option, the median of the answers to items 1, 3 and 6 of that patient was imputed as the score for items 4 and 5.

(b) For items 4, 5, 6 and 11 concerning difficulties taking care of teeth, altered dentition, retracted lips/sunken cheeks and altered appearance, patients felt the score range 'never-always' was inappropriate. They argued that the symptom is 'either present or not'. In accordance with their comment, instead of 'never-always' a score range '0 (totally disagree), 1 (disagree), 2 (no opinion), 3 (agree) and 4 (totally agree)' was formulated.

The resulting final version of the Dutch MHISS is shown in the Appendix.

Patients

For this study, consecutive patients attending the outpatient clinic or the day care unit of the Department of Rheumatology of the Leiden University Medical Center in the study period were invited by the investigators (AAS, ES, AJ) to take part in the study. None of the patients refused participation. Inclusion criteria were: diagnosis SSc according to the criteria as set by the American College of Rheumatology criteria (14) and/or Leroy & Medsger criteria (15), age older then 18 year and fluently speaking Dutch. The disease duration (years), presence of Raynaud's phenomenon (years), disease subset (limited or diffuse SSc), organ involvement (cardiac, pulmonary, gastro-intestinal, renal) and presence of other auto-immune manifestations (primary biliary cirrhosis, thyroiditis) were derived from the medical record (table 1). The local medical ethics committee approved the protocol, and all patients gave written informed consent.

Assessments

Apart from the Dutch MHISS, the following assessments were done:

(a) Objective xerostomia (mouth dryness)

For the measurement of saliva production, the Saxon test was used (16). Patients were asked to swallow before initiation of the test, and next chew on a dry gauze sponge (10x 10 cm) for two minutes without swallowing. After the two minutes the gauze placed in a tube, and the amount of produced saliva was determined by subtracting the original weight of the gauze and weight of the tube from the weight obtained after chewing. Objective xerostomia is considered present if the saliva production is less than 2.75 grams (16)

(b) Objective xerophthalmia

Xerophthalmia was measured by the Schirmer's test: Two small pieces of sterile filter papers were inserted into the lateral third in each lower eyelid, for a maximum of 5 minutes. Patients were asked to close the eyes. Wetting of less than 5 mm in five minutes of both eyes was considered abnormal (17).

(c) Subjective xerophthalmia *and xerostomia*

Two VAS scores consisted of a 100 mm horizontal line, ranging from 0 on the left anchor being no symptoms, to 100 on the right anchor with the worst imaginable symptoms.

(d) Maximal mouth opening

For the maximal mouth opening the inter-incisor distance was measured in millimeter with a digital caliper (18). In case the mouth restriction was determined by the lips, the

Table 1. Demographic and disease characteristics of 52 patients with systemic sclerosis

Age (year); mean (SD)	55 (21)
Female ; %	41 (79)
Smoking; %	4 (8)
HAQ (range 0-3); mean (SD)	0.83 (0.68)
ESR (mm); mean (SD)	21 (21)
Diffuse subtype SSc (%)	27 (52)
Disease duration, (year) median (25^{th}-75^{th}percentile)	5 (2-10)
Raynaud phenomenon present (%)	48 (92)
Digital ulcers present (%)	33 (64)
Maximal Mouth Opening (mm), mean (SD)	38.7 (10.1)
Autoantibodies (%)	
anti-centromere	13 (25)
anti-Scl70	19 (36)
anti-SSA	6 (11,5)
anti-SSB	2 (3,8)
Xerophthalmia	
subjective (VAS 0-100 mm); median (25^{th}-75^{th}percentile)	1.5 (0-37)
objective; schirmer's test [a] (%)	19 (36,5)
Xerostomia	
subjective (VAS 0-100 mm); median (25^{th}-75^{th}percentile)	19 (0-58)
objective; saxon test (gram)[b] ; mean (SD)	9 (17%)
Organ involvement (%)	
heart involvement	1 (1,9)
interstitial lung disease	28 (53,8)
gastrointestinal involvement	35 (67,3)
renal crisis	5 (9,6)
pulmonary hypertension	4 (7,7)
Other autoimmune manifestations (%)	
primary biliary cirrhosis	6 (11,5)
anti-mitochondrial antibodies	4 (7,7)
anti-smooth muscle antibodies	3 (5,8)
thyroiditis	4 (7,7)
anti-TPO antibodies	4 (7,7)
anti-thyroglobulin antibodies	4 (7,7)

HAQ Health Assessment Questionnaire; ESR =Erythrocyte Sedimentation Rate; [a] Insufficient tear production if both eyes <5mm; [b] insufficient if saliva production <2.75 gram.

maximal mouth opening was measured as the distance between the nearest points of the two vermillion borders in the sagittal plane.

(e) Overall physical functioning

To assess the overall level of physical functioning, the Systemic Sclerosis Health Assessment Questionnaire (SSc-HAQ) was filled in, a 20-item questionnaire comprising eight domains of activities of daily living with the final score ranging from 0 (no disability) to 3 (severe disability) and five scleroderma-symptom visual analogue scales (VAS); Raynaud's disease, digital ulcers, intestinal complaints, pulmonary complaints, overall complaints, and pain. The SSc HAQ was found to be a reliable outcome measure for disease severity in SSc (19).

Statistical analysis

Statistical analyses were executed using SPSS 16.0 software. All continuous variables were expressed as means and standard deviations, or as medians and Inter Quartile Ranges (IQR), according to their distributions. Missing data for demographic and disease characteristics were not listed, unless more then 5% present.

Internal consistency

The internal consistency of the Dutch MHISS (the extent to which the different items are correlated) was determined by calculating Cronbach's alpha for both the total scale and two subscales (not for aesthetic concerns as this subscale has only 2 items). The internal consistency is considered to be good when Cronbach's alpha is between 0.70 and 0.95 (20).

Construct validity

Two aspects of construct validity were used: discriminative or divergent validity (to be able to distinguish between 'known groups' with expected differences in scores) and convergent validity (how strongly a measure correlates with other related measures). To test the discriminative validity we hypothesized that patients with more global disability, smaller maximal mouth opening, more subjective as well as objective xerostomia would have higher MHISS scores. We dichotomized measures of global as well as mouth disability in two groups according (a) below and above median value (HAQ score, maximal mouth opening and subjective xerostomia (VAS score) scores) and (b) below and above 2.75 gram (objective xerostomia; considered cut-off score for normal saliva production). The Dutch MHISS scores were compared between the two groups using the independent Student t-test.

To test the convergent validity, Spearman rank correlation coefficients were used to assess the correlation between the Dutch MHISS and measures of mouth symptoms or overall disability. We hypothesized that the Dutch MHISS score would be increased

in patients with more subjective xerostomia, more limitation of the mouth opening (decreased maximal mouth opening), more objective xerostomia (decreased saliva production) or more overall disability (increased HAQ). Spearman's correlation was interpreted as excellent (>0.91), good (0.90–0.71), moderate (0.70–0.51), fair (0.50–0.31), or little or absent (<0.30) (21).

Test-retest reliability

Intra-class correlation coefficients (ICC) were computed between the scores of the first and second questionnaire, with a value of >0.70 being considered the minimum acceptable value (20)

Results

Validity

The disease characteristics of the 52 participants are shown in Table 1. All participants returned both the Dutch MHISS questionnaires. There were no missing data in either the first or second returned MHISS questionnaires. The mean as well as median Dutch MHISS score was 17.5 (SD 10.0, range 0-41, two patients with score 0, one patient with score 41). With item 4 and/or 5, eleven patients reported having dentures. The Dutch MHISS scores were not significantly different between patients with diffuse or limited SSc (mean 17.2 versus 17.8, p=0.842).

Internal consistency

The internal consistency of the Dutch MHISS total as well as different survey items was found to be adequate (20). Cronbach's alpha was 0.88 for the total MHISS score, 0.86 for the factor 'mouth opening (items 1, 3, 4, 5 and 6), and 0.79 for the factor mouth dryness (items 7, 8, 9 and 10).

Construct validity

With respect to divergent validity, a significantly higher mean Dutch MHISS score was seen in patients with more global disability, more subjective xerostomia, more limitation of the mouth opening and more objective xerostomia (Table 2).

Table 2: Dutch MHISS scores (SD) compared between patients with low and high[1] HAQ, maximal mouth opening, subjective and objective xerostomia scores

	MHISS		
	Low group	High group	P value[a]
Health Assessment Questionnaire (HAQ)	11.2 (7.6)	22.8 (8.5)	0.000
Maximal mouth opening (MMO)	21.5 (9.6)	13.5 (9.4)	0.004
Subjective xerostomia[b]	11.4 (7.4)	22.9 (9.0)	0.000
Objective xerostomia[c]	26.9 (9.2)	15.4 (9.8)	0.002

For HAQ, MMO, subjective xerostomia two groups defined as ≤ median and >median, for objective xerostomia low and high groups defined as ≤ 2.75 gram and >2.75 gram; [a] independent sample t-test; [b] Visual analogue scale for mouth dryness in the past 3 months; [c] Saxon test.

Regarding convergent validity, moderate to good correlations were seen between the Dutch MHISS and maximal mouth opening, subjective xerostomia and the HAQ score, whereas there was no association with objective xerostomia. (Table 3)

Table 3: Spearman rank correlation coefficient between mouth handicap (as measured by the Dutch MHISS) and diability (as measured by HAQ), maximal mouth opening, subjective and objective xerostomia

Health Assessment Questionnaire (HAQ)	0.599	p=0.000
Maximal mouth opening (MMO)	-0.518	p=0.000
Subjective xerostomia[a]	0.536	p=0.000
Objective xerostomia[b]	-0.200	p=0.177

[a] Visual analogue scale for mouth dryness in the past 3 months; [b] Saxon test.

Test-retest reliability

Fourty-nine patients filled in a second Dutch MHISS after two weeks. The mean MHISS score of the second measurement was 16.5 (SD 10.0), (p-value 0.229 as compared to the first measurement, paired t-test). The ICC was 0.94 (p=0.000), demonstrating excellent reliability (20).

Discussion

This study aimed to translate, adapt and validate the MHISS into the Dutch language. The properties of the Dutch MHISS regarding internal consistency, construct validity and test-retest reliability were found to be good, and comparable with the original version.

In order to warrant equivalence of measurement in the Dutch language, international guidelines for cross cultural adaptation of health related measures were used. In this process small adaptations to the original French version were made, including adding

a response option 'not applicable' for the questions regarding dental hygiene. The fact that none of the patients in the original study (10) reported having dentures is remarkable. In the Netherlands, 27% of the persons (55-74 year of age) reported having dentures (22). The number of patients with dentures in our cohort (11/52) seems comparable with this proportion. In our study, it remained unknown if the presence of a denture was caused by SSc or other reasons.

The mean Dutch MHISS total score in our patient group was comparable with the score of the original MHISS study (18.8 (SD 10.2) versus 20.3 (SD 9.7), despite differences in the patient characteristics: patients in the present study had a shorter disease duration (7.2 (SD 7.3) versus 13.7 (12.3) years), demonstrated less limitations in daily activities as measured by the HAQ (0.83 (SD 0.68) versus 1.20 (SD 0.68), but had a comparable maximal mouth opening as compared to the original study. In other studies similar values of the MHISS were found (10;23).

The test-retest reliability of the Dutch MHISS was excellent and comparable with the measurement properties described for the original MHISS (10) . The internal consistency for the total score as well as two of the three factors ('mouth handicap' and 'sicca') were good, and confirm the results of the previous factor analysis.

In our study a good discriminative validity was demonstrated as the Dutch MHISS was significantly increased in patients with more global disability (HAQ), more subjective xerostomia, more limitation of the mouth opening and more objective xerostomia. Analysis of convergent validity resulted in remarkably better correlation in the total Dutch MHISS score with measures of overall physical functioning and maximal mouth opening compared with the original MHISS.

A limitation of this study is the fact that the Dutch-MHISS was not compared with other measures of disability (physical or mental function) as was previously done (11). However, considering the good correlations of the Dutch MHISS with other relevant disability outcomes, good construct validity was demonstrated. The patients participating in this study were treated in a tertiary care hospital, whereas in the validation study by Mouthon all patients were assessed during the annual meeting of the French SSc patients association. Interestingly, it has recently been reported that association patients had significantly increased disability of the mouth (MHISS 20.65 ± 10.8 vs 13.25 ± 9.3; p=0.0001) and impaired hand and wrist mobility (Kapandji score 38.05 ± 10.26 vs 43.90 ± 8.26, p=0.001) as compared with hospitalized patients (24) Therefore, a selection bias cannot be excluded. For a proper judgment of the applicability of the questionnaire, a validation in a more general population of SSc patients with possibly less disease severity is desirable. A remarkable finding in our study was the relatively low mean value of the mean VAS xerophthalmia as compared with the 19% of patients with abnormal Schirmer testing. An explanation for the asymptomatic presence of xerophthalmia is not easily found. It may however underline the need for an objective measure for xerophthalmia.

In conclusion, we have successfully translated and adapted the MHISS into the Dutch language, with the final Dutch version demonstrating good psychometric properties. Research on the validity in other SSc populations as well as the responsiveness of the questionnaire in treatment settings is warranted.

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Reference List

(1) Medsger TA, Jr. 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(2):255-73, vi.

(2) Mehra A, Kumar S. Periodontal manifestations in systemic sclerosis: a review. Dent Today 2008; 27(6):50, 52, 54.

(3) Albilia JB, Lam DK, Blanas N, Clokie CM, Sandor GK. Small mouths ... Big problems? A review of scleroderma and its oral health implications. J Can Dent Assoc 2007; 73(9):831-6.

(4) Rosenthal IH. Generalized scleroderma; hidebound disease, its relation to the oral cavity, with case history and dental restoration. Oral Surg Oral Med Oral Pathol 1948; 1(11):1019-28.

(5) Swaminathan S, Goldblatt F, Dugar M, Gordon TP, Roberts-Thomson PJ. Prevalence of sicca symptoms in a South Australian cohort with systemic sclerosis. Intern Med J 2008; 38(12):897-903.

(6) Salliot C, Mouthon L, Ardizzone M, Sibilia J, Guillevin L, Gottenberg JE et al. Sjogren's syndrome is associated with and not secondary to systemic sclerosis. Rheumatology (Oxford) 2007; 46(2):321-6.

(7) Lambert M, Tomasi JP, Peeters A. Sjogren's syndrome associated with CREST and positive antibodies to Ro(SSA)/La(SSB). J Rheumatol 1993; 20(1):203-4.

(8) Pizzo G, Scardina GA, Messina P. Effects of a nonsurgical exercise program on the decreased mouth opening in patients with systemic scleroderma. Clin Oral Investig 2003; 7(3):175-8.

(9) Maddali BS, Del RA, Galluccio F, Tai G, Sigismondi F, Passalacqua M et al. Efficacy of a tailored rehabilitation program for systemic sclerosis. Clin Exp Rheumatol 2009; 27(3 Suppl 54):44-50.

(10) Mouthon L, Rannou F, Berezne A, Pagnoux C, Arene JP, Fois E et al. Development and validation of a scale for mouth handicap in systemic sclerosis: the Mouth Handicap in Systemic Sclerosis scale. Ann Rheum Dis 2007; 66(12):1651-5.

(11) Maddali BS, Del RA, Miniati I, Galluccio F, Landi G, Tai G et al. The Italian version of the Mouth Handicap in Systemic Sclerosis scale (MHISS) is valid, reliable and useful in assessing oral health-related quality of life (OHRQoL) in systemic sclerosis (SSc) patients. Rheumatol Int 2012; Sep;32(9):2785-90

(12) Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine 2000; 25(24):3186-91.

(13) Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. J Clin Epidemiol 1993; 46(12):1417-32.

(14) Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980; 23(5):581-90.

(15) LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Jr. et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988; 15(2):202-5.

(16) Kohler PF, Winter ME. A quantitative test for xerostomia. The Saxon test, an oral equivalent of the Schirmer test. Arthritis Rheum 1985; 28(10):1128-32.

(17) Vitali C. Classification criteria for Sjogren's syndrome. Ann Rheum Dis 2003; 62(1):94-5.

(18) Wood GD, Branco JA. A comparison of three methods of measuring maximal opening of the mouth. J Oral Surg 1979; 37(3):175-7.

(19) Clements PJ, Wong WK, Hurwitz EL, Furst DE, Mayes M, White B et al. The Disability Index of the Health Assessment Questionnaire is a predictor and correlate of outcome in the high-dose versus low-dose penicillamine in systemic sclerosis trial. Arthritis Rheum 2001; 44(3):653-61.

(20) Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol 2007; 60(1):34-42.

(21) Fermanian J. [Measuring agreement between 2 observers: a quantitative case]. Rev Epidemiol Sante Publique 1984; 32(6):408-13.

(22) A.A.Schuller. Mondgezondheid volwassenen, KvL/GL/2009.048 TNO, Nederlande organisatie voor toegepast natuurwetenschappelijk onderzoek. Ref Type: Online Source

(23) Bongi SM, Del RA, Galluccio F, Sigismondi F, Miniati I, Conforti ML et al. Efficacy of connective tissue massage and Mc Mennell joint manipulation in the rehabilitative treatment of the hands in systemic sclerosis. Clin Rheumatol 2009; 28(10):1167-73.

(24) Mestre-Stanislas C, Poiraudeau S, Berezne A, Rannou F, Pagnoux C, Revel M et al. Differences in patients with systemic sclerosis recruited from associations and tertiary care settings. Presse Med 2010; 39(9):e205-e209.

Appendix.

English MHISS scale (10)

		0	**1**	**2**	**3**	**4**
1	I have difficulties opening my mouth	**0**	**1**	**2**	**3**	**4**
2	I have to avoid certain drinks (sparkling, alcohol, acidic)	**0**	**1**	**2**	**3**	**4**
3	I have difficulties chewing	**0**	**1**	**2**	**3**	**4**
4	My dentist has difficulties taking care of my teeth	**0**	**1**	**2**	**3**	**4**
5	My dentition has become altered	**0**	**1**	**2**	**3**	**4**
6	My lips are retracted and/or my cheeks are sunken	**0**	**1**	**2**	**3**	**4**
7	My mouth is dry	**0**	**1**	**2**	**3**	**4**
8	I must drink often	**0**	**1**	**2**	**3**	**4**
9	My meals consist of what I can eat and not what I would like to eat	**0**	**1**	**2**	**3**	**4**
10	I have difficulties speaking clearly	**0**	**1**	**2**	**3**	**4**
11	The appearance of my face is modified	**0**	**1**	**2**	**3**	**4**
12	I have trouble with he way my face looks	**0**	**1**	**2**	**3**	**4**

0=never; 1=rarely; 2=occasionally; 3=often; 4=always.

French generic MHISS scale supplied by L.Mouthon

		0	**1**	**2**	**3**	**4**
1	Je suis géné(e) pour ouvrir la bouche	**0**	**1**	**2**	**3**	**4**
2	Je dois éviter certaines boissons (gazeuses, alcoolisées, acides)	**0**	**1**	**2**	**3**	**4**
3	J'ai des difficultés à mastiquer	**0**	**1**	**2**	**3**	**4**
4	Mon dentiste a des difficultés à effectuer les soins	**0**	**1**	**2**	**3**	**4**
5	L'état de mes dents s'est dégradé	**0**	**1**	**2**	**3**	**4**
6	Mes lèvres et/ou mes joues sont rétractées	**0**	**1**	**2**	**3**	**4**
7	Ma bouche est sèche	**0**	**1**	**2**	**3**	**4**
8	Je dois boire souvent	**0**	**1**	**2**	**3**	**4**
9	Je suis obligé(e) de choisir mon alimentation en fonction de ce que je peux manger et non en fonction de ce que j'ai envie de manger	**0**	**1**	**2**	**3**	**4**
10	Je suis géné(e) pour articuler les mots	**0**	**1**	**2**	**3**	**4**
11	L'apparence de mon visage s'est modifiée	**0**	**1**	**2**	**3**	**4**
12	J'ai une gène esthétique	**0**	**1**	**2**	**3**	**4**

0= Jamais ; 1=Rarement ; 2=Régulièrement ; 3=Souvent ; 4= Toujours

Dutch MHISS scale

1	Ik vind het lastig om mijn mond te openen	**0**	**1**	**2**	**3**	**4**	
2	Ik moet bepaalde dranken vermijden (bruisende, alcoholische en/of zure dranken)	**0**	**1**	**2**	**3**	**4**	
3	Ik heb moeite met kauwbewegingen	**0**	**1**	**2**	**3**	**4**	
7	Ik heb een droge mond	**0**	**1**	**2**	**3**	**4**	
8	Ik moet vaak drinken	**0**	**1**	**2**	**3**	**4**	
9	Ik moet mijn voedsel kiezen op grond van wat ik kan eten, en niet op grond van waar ik *zin* in heb	**0**	**1**	**2**	**3**	**4**	
10	Ik vind het lastig om te articuleren (woorden duidelijk uit te spreken)	**0**	**1**	**2**	**3**	**4**	
12	Ik voel mij niet prettig met mijn uiterlijk	**0**	**1**	**2**	**3**	**4**	
4	Mijn tandarts heeft moeite om mijn gebit te behandelen	**0***	**1***	**2***	**3***	**4***	**NA**
5	De toestand van mijn gebit is verslechterd	0*	**1***	**2***	**3***	**4***	**NA**
6	Mijn lippen en/of mijn wangen zijn strak getrokken	0*	**1***	**2***	**3***	**4***	
11	Het uiterlijk van mijn gezicht en mond is veranderd	0*	**1***	**2***	**3***	**4***	

0= Nooit ; 1= Zelden ; 2= Regelmatig ; 3= Vaak ; 4= Altijd; 5=gebitsprothese; 0*= helemaal oneens; 1*= oneens; 2*=neutraal; 3*=eens; 4*=helemaal eens; NA= not aplicable

CHAPTER 5

Validity and responsiveness of the Michigan Hand Questionnaire in patients with Systemic Sclerosis

Submitted

A.A.Schouffoer, F.J. van der Giesen, L.J.J. Beaart-van de Voorde, T.W.J. Huizinga, R. Wolterbeek, T.P.M. Vliet Vlieland.

Abstract

Objective

To assess the validity and responsiveness of the Michigan Hand Questionnaire (MHQ) in patients with Systemic Sclerosis (SSc).

Methods

Data were gathered in connection with a randomized, controlled trial comparing the effectiveness of a 12-week multidisciplinary team-care programme, including a handfunction treatment module, with regular care. All fifty-three patients (28 intervention group and 25 control group) completed the MHQ (including 6 domains: function, activities of daily living, pain, work, aesthetics, and satisfaction) at baseline and after 12 weeks. Other measures included the HAQ (Health Assessment Questionnaire), Hand Mobility in Scleroderma (HAMIS), Sequential Occupational Dexterity Assessment (SODA), grip strength, pinch grip and Modified Rodnan Skin Score (MRSS). Validity was determined by computing Spearman correlation coefficients between the baseline MHQ total score and subscales and other measures of (hand)disability. Responsiveness in the intervention group was evaluated by the standardized response mean (SRM), effect size (ES), and responsiveness ratio (RR). In addition, pooled ES for the difference between the two groups were computed.

Results

Significant correlations were seen between the MHQ total score and the HAQ (r=-0.62), HAMIS (r=-0.54), SODA (r=0.47), SODA Pain (r=0.32) and MRSS (r=0.46). The ES of the MHQ total score within the intervention group was 0.49, which was larger than those of all other outcome measures. Similar results were obtained for the SRM and RR. The pooled ES of the difference between intervention and control groups for the MHQ total score was 0.86.

Conclusion

The MHQ demonstrated adequate validity and responsiveness in patients with SSc.

Introduction

Systemic sclerosis (scleroderma, SSc) is a chronic multi-system disease that may result in significant disability and impaired health related quality of life (1;2). In patients with SSc hand function is often impaired (3). Increased skin thickness, impaired range of motion in flexion and extension, digital ulcers, arthritis, loss of strength and Raynaud's phenomenon may contribute to limitations in activities involving the hands. In addition to function, the altered appearance of the hands is an important feature in SSc, as a result of fibrosis, contractures, vascular complications and teleangieectasia.

Given the significance of hand function disability in SSc, outcome measures with good clinimetric properties are needed to assess disease evolution and treatment efficacy in this patient group. Hand function in SSc patients can been evaluated by means of generic questionnaires including the Cochin Hand Function Scale (CHFS) (4),) as well as performance tests as the Hand Function in Systemic Sclerosis (HAMIS) (5), Hand Anatomic Index (HAI) (6;7), the delta finger-to-palm (FTP)(8), Kapandji indexes (9;10) and pinch grip and grip strength (11). Some of these were evaluated with respect to responsiveness over time (12), and others concerning their ability to detect treatment effect in patients with SSc(11;13;14).

All of the abovementioned hand function instruments used in SSc do however not capture important aspects of hand function in SSc such as aesthetics, satisfaction with hand function and pain. Moreover, performance tests may be less suitable in routine care due to the required training and equipment for their use. The Michigan Hand outcomes Questionnaire (MHQ) is a self-reported, self-administered questionnaire that contains 37 items and requires approximately 15 minutes completing. It yields an overall summary score of hand function, as well as scores for 6 specific scales: hand function, ability to complete activities of daily living, pain, work performance, aesthetics, and patient satisfaction. The MHQ (15) was listed in a provisional core set of measures for assessment of disease activity and severity in clinical trials of SSc (16). It has however never been used for this purpose, since its validation in SSc patients has not completely been investigated yet (17). In contrast, in rheumatoid arthritis the clinimetric properties of the MHQ have been extensively documented (18).

Our aim was therefore to examine the validity of the MHQ in patients with SSc and its responsiveness to change.

Patients and methods

Study design and participants

The subjects were participants in a randomized controlled clinical trial comparing a 12-week multidisciplinary team care programme with regular outpatient care. This study was conducted at the Leiden University Medical Center (19). Inclusion criteria were:

SSc according to Leroy's criteria (20), age 18-75 year, being able to cycle on a bicycle ergo meter, stable anti-inflammatory medication over the past 2 months, and fluency in Dutch. Exclusion criteria were: cardio-pulmonary screening resulting in contra-indications for physical exercises, engagement in another exercise therapy program and concomitant diseases interfering with ADL activities. Fifty-three patients were included; twenty-eight patients were randomly assigned to the intervention group and twenty-five to the control group. Measurements took place at baseline, after 12 weeks and 24 weeks. For the present study only the baseline and 12-week data were used.

Intervention and control condition

The multidisciplinary team care programme is described in detail in a previous publication. In brief, it consisted of standardized group sessions provided once per week in a day patient care setting. The group sessions included general exercises, hand/mouth exercises and educational sessions. In addition, depending on the patients' individual needs, individual treatments by the rheumatologist and health professionals were scheduled. Apart from the weekly treatment in the clinic, patients were required to participate in individual supervised exercises provided by a physical therapist near their own home in a private practice once a week and to perform a home-based exercise programme on at least 6 days per week.

The hand exercises were to be performed daily, with each session lasting 10 minutes. During an exercise session the following angular motions were performed: opposition and reposition of the thumb, flexion and extension of the fingers, abduction an adduction of the fingers and making a fist. Active exercises were performed using the patient's own muscle strength to stretch limited tissues, for example making a fist aiming to elongate dorsal skin on the fingers. In the passive exercises external forces were used to elongate limited tissues, for example, to stretch the fingers in extension the other hand was used to press the open hand on a flat surface like a table. In each session every muscle group that was related to limited motion was stretched for 10 seconds in 3 repetitions. Exercise materials, like squeeze balls, were used according to the patient's preferences and needs. The intensity of the stretching was monitored by recording discomfort and pain directly after the treatment session. If needed, the intensity was adjusted so that the discomfort or pain was at the patient's normal level within 15 minutes after performing the exercises. To increase exercise compliance patients were instructed to monitor their own progress in hand range of motion. For this purpose callipers were provided to measure the distance between the fingertip and the proximal skin crease in the palm of the hand, as a measure of finger flexion. These measurements were recorded during the supervised sessions by the patient in a hand exercise diary, which also contained the exercise instructions.

The control condition included regular outpatient care, to be determined by the treating rheumatologist.

Assessments

Data were gathered by means of review of the medical records, questionnaires, physical examinations and additional examinations consisting of laboratory tests. All clinical assessments were done by AAS.

Disease characteristics

Disease characteristics were derived from the medical record and included: disease subset (limited or diffuse) the number of years since onset of Raynaud's, the Modified Rodnan Skin Score (MRSS), auto-antibody profile , erythrocyte sedimentation rate (mm/hr) , C-reactive protein (mg/l), presence of interstitial lung disease or cardiac involvement (yes/no)

General physical functioning

The SSc-Health Assessment Questionnaire (SSc-HAQ) is a 20-item questionnaire comprising eight domains of activities of daily living, with the final score ranging from 0 (no disability) to 3 (severe disability) and five visual analogue scales (21), Raynaud's disease, digital ulcers, intestinal complaints, pulmonary complaints, overall complaints, and pain. The SSc-HAQ score was calculated using the aids/devices. It has been found to be a reliable outcome measure for disease severity in SSc (22). In addition, a Dutch HAQ-translation demonstrated good psychometric properties (23). The SSc-HAQ (8;24;25) is most frequently used to assess general disability. Hand disability has been shown to contribute to 75% of the HAQ variance in patients with SSc (10).

Measures of hand function

The Michigan Hand outcome Questionnaire(MHQ) . The MHQ is a 57-item questionnaire covering 6 domains: (1) overall hand function, (2) activities of daily living, (3) pain, (4) work performance, (5) aesthetics, and (6) patients' satisfaction with hand function. Pain, work performance, aesthetics and satisfaction are scored for the right and left hands separately. The scoring method is described by the original authors of the MHQ (15). Each item is scored on a 1 to 5 scale, for each domain the sum of the responses of each item is converted into a scale ranging from 0 to 100. If both hands are affected the left and right-hand scale scores are averaged to get the score. A higher score indicates a better hand function, except for the pain domain where a higher score means more pain. The total score (the average of all domains) ranges from 0 to 100, with a higher score indicating a better hand function.

The Hand Mobility in Scleroderma (HAMIS) test. The HAMIS test consists of 9 items graded on a scale of 0-3, the final score ranges from 0 (normal function) to 27 (severe immobility). Each hand is assessed separately. Good clinometric properties were demonstrated (5;26).

Sequential Occupational Dexterity Assessment (SODA). The SODA is a performance measure of dexterity (27). With the SODA, patients performs 12 standardized tasks (6 bimanual and 6 one-handed) representing all major grips such as pinch grip, cylindrical grip, and writing grip. The assessor scores whether it is possible to perform the task in the standardized way, the effort that the activity takes, and the pain patients experiences when performing the task. The combination of the possibility to perform the tasks and the effort and pain scores forms the SODA score, ranging from 0 to 108, with a higher number meaning better hand function. The pain patients experience when performing the tasks forms the SODA pain score, ranging from 0 to 12, with a higher score indicating more pain. The SODA proved to be reliable, valid, and responsive to clinical changes in patients with RA (27).

Grip-strength and Pinch grip (kg) The grip strength and pinch grip were measured with a Jamar dynamometer (R. Harkonen, j hand ther, 1993). After testing twice, the highest score of both hands was registered. For this study the right hand scores were used.

Subjective opinion about change of hand function. At the follow-up assessment patients were asked to rate the changes in hand function by means of a 5-point Likert-scale (1, much worsened; 2, worsened; 3, not changed; 4, improved; 5, much improved).

Statistical analysis

Data are presented as mean values with standard deviation. In case of skewed distribution a median and interquartile range were used.

The internal consistency of the MHQ pertains to the extent to which the different subscales and subscale items are correlated. It was determined by calculating Cronbach's alpha. The internal consistency is considered to be good when Cronbach's alpha is between 0.70 and 0.95 (28). Pearson's correlation coefficients of each subscale against the other subscales within the MHQ were determined to establish if the subscales behave in an expected manner.

To test the convergent validity, Spearman rank correlation coefficients were used to assess the correlation between the MHQ total score and subscale scores on the one side and other measures of (hand) disability on the other side. We hypothesized that the MHQ score would be worse in patients with more overall functional disability (HAQ), a worse hand function as measured with the HAMIS, grip strength and pinch grip strength and SODA, and more severe skin involvement. Correlation coefficients were interpreted as small (0.10-0.29), medium (0.30-0.49) or large (0.50-1.0).

To determine the responsiveness to changes over time, in both the intervention and control groups for all clinical measures mean change scores were calculated (baseline minus follow-up) with the 95% confidence intervals (CIs). Responsiveness within the intervention group was evaluated by means of various methods (29;30) the standardized

response mean (SRM) pre-treatment mean – post treatment mean divided by the SD of the change score), the effect size (ES) (pre-treatment mean – post treatment mean divided by the SD of the pre-treatment mean) (31), and Guyatt's responsiveness ratio (the mean change score of the improved patients divided by the SD of the baseline score in stable patients) (29). For the responsiveness ratio, patients were divided into improved, stable, or deteriorated according to their subjective opinions of changes in hand function on a Likert scale. For this purpose, the scores were recoded as follows: 1 and 2 equals deteriorated, 3 equals stable and 4 and 5 equals improved. A negative value of the SRM, effect size, or responsiveness ratio indicates that the mean baseline score was smaller than the mean follow-up score. Values of .20, .50, and .80 or higher were considered to represent small, moderate, and large responsiveness for all 3 measures of responsiveness, respectively (30) however, for the responsiveness ratio a cut off point of 1.96 for sufficient responsiveness has also been reported (28). For the SRM, values of 0.2 to 0.3 could be found in evaluating the effect of a placebo, values of 0.3 to 0.5 in assessing the effect of a moderately active drug, and large values of 1.0 or greater in evaluating the effects of surgical procedures (32). The treatment effect of the MHQ was calculated with a pooled ES; the difference of the mean change score of the intervention group and the control group, divided by the pooled SD of the change scores of the two groups (33) .

Results

The characteristics of the patients are described in Table 1. Of the 53 patients included, 28 patients were allocated to the intervention group, of which 25 completed the multidisciplinary team care programme and the assessment at 12 weeks. Twenty five patients were allocated to the control group, of whom 24 were assessed at 12 weeks.

Table 2 shows the baseline MHQ subscale and total scores in the total group. The MHQ demonstrated good internal consistency with high Cronbach's alpha scores ranging from 0.720 in the aesthetic subscale for the right hand to 0.922 in the work subscale. Cronbach's alpha score for the MHQ total score was 0.860. In the subscale pain a 'floor effect' was observed with a minimal score of 0 in 16 percent of the patients (34).

Table 3 demonstrates the correlation coefficients of each scale against the other scales in the MHQ. Most of the correlations were found to be moderate to large, except for the aesthetic subscale, indicating that this subscale measures something different from the other subscales.

In Table 4 the correlations between the baseline MHQ subscale and total scores and other measures of (hand) function are shown. Overall, the correlations between the MHQ scores for the subscales overall hand function, activities of daily living, work performance and satisfaction and the MHQ total score on the one side and the HAQ,

Table 1. Baseline characteristics of 53 patients with systemic sclerosis participating in a randomized controlled trial comparing a 12-week multidisciplinary treatment program with usual outpatient care.

	Total group N=53	Intervention group N=28	Control group N=25
Sex, Female No. (%)	40 (76)	19 (68)	21 (84)
Age, years, mean (SD)	52.9 (10.7)	53.9 (10.8)	51.7 (10.8)
Right handed, no (%)	47 (89)	26 (96)	21 (88)
Disease subset: diffuse SSc, no (%)	30 (57)	15 (54)	15 (60)
Time since onset Raynaud phenomenon, years, median (IQR)	9.2 (11.8)	8.6 (12.7)	10.2 (12.8)
MRSS‡ (0-51), median (IQR)	3 (6)	4 (7)	3 (5)
Auto-antibodies (% positive)			
ANA	49 (93)	26 (93)	23 (92)
Anti-Scl70	20 (38)	10 (36)	10 (40)
Anti-Centromere	8 (15)	3 (11)	5 (20)
ESR♦ mm/hr, median (IQR)	17 (21)	14 (19)	20 (30)
CRP◊, median (IQR)	4 (5.)	3 (3)	5 (7)
Health Assessment Questionnaire, mean (SD)	0.77 (0.57)	0.81 (0.66)	0.73 (0.46)
VAS Raynaud's phenomenon (0-100 mm), median (IQR)	39 (42)	46 (40)	33 (50)
VAS Digital ulcers (0-100 mm), median (IQR)	7 (26)	9 (40)	2 (17)
VAS Pain (0-100 mm), median (IQR)	21 (38)	20 (43)	23 (39)

SSc= systemic sclerosis; IQR=interquartile range; dcSSc= diffuse cutaneous SSc; MRSS=modified Rodnan skin score; ANA=antinuclear antibody; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; VAS=Visual Analogue Scale.

Table 2: Michigan Hand Questionnaire subscale and total scores and internal consistency in 53 patients with systemic sclerosis

	Score	Cronbach's α
MHQ Overall Hand Function		
Right	56.6 (16.5)	.881
Left	57.4 (17.5)	.892
MHQ Activities of daily living		
Right	81.5 (16.0)	.805
Left	78.9 (20.8)	.877
Both hands	77.1 (19.4)	.896
MHQ Work performance	63.4 (22.6)	.922
MHQ Pain	37.9 (25.8)	.761
MHQ Aesthetics		
Right	67.0 (19.3)	.720
Left	68.0 (21.6)	.793
MHQ Patient satisfaction		
Right	50.0 (23.9)	.881
Left	50.0 (26.0)	.923
MHQ Total	59.7 (11.3)	.860

Table 3: Correlation* between the subscales and total MHQ in 53 systemic sclerosis patients participating in a randomized controlled clinical trial.
***Pearson's correlation coefficients: small (0.10-0.29), medium (0.30-0.49) or large (0.50-1.0)**

	Function	ADL	Work performance	Pain	Aesthetics	Patient satisfaction
Function	-					
ADL	.69	-				
Work performance	.67	.64	-			
Pain	-.65	-.56	-.57	-		
Aesthetics	.30	.32	.40	-.12	-	
Patient satisfaction	.79	.60	.67	-.59	.35	-
Total MHQ	.77	.73	.82	-.34	.66	.81

* MHQ= Michigan Hand Questionnaire; ADL = activities of daily living.

Table 4: Spearman R correlation coefficients between the MHQ subscale and total scores and measures of (hand) disability in 53 patients with systemic sclerosis

	HAQ	HAMIS	Grip strength	Pinch Grip	SODA	SODA pain	MRSS
MHQ Function	-0.416**	-0.492**	0.127	0.140	0.363*	-0.380*	-0.520**
MHQ Activities of daily living	-0.734**	-0.582**	0.442**	0.449**	0.641**	-0.456**	-0.534**
MHQ Work performance	-0.630**	-0.505**	0.273	0.247	0.433**	-0.420**	-0.470**
MHQ Pain	0.240	0.243	0.039	0.008	-0.271	0.423	0.442
MHQ Aesthetics	-0.269	-0.229	0.070	0.088	0.316	-0.165	-0.197
MHQ Patient satisfaction	-0.457**	-0.383**	0.114	0.115	0.361*	-0.218	-0.424**
MHQ total	-0.623**	-0.538**	0.259	0.265	0.472**	-0.319*	-0.457**

MHQ= Michigan Hand Questionnaire; HAQ=Health Assessment Questionnaire; HAMIS= Hand Mobility In Scleroderma; SODA= Sequential Occupational Dexterity Assessment; MRSS=Modifies Rodnan Skin Score; *p <0.05; **p <0.01,

HAMIS, SODA scores and MRSS on the other side were moderate. Correlations of these scores with pinch and grip strength and SODA pain were however low. The MHQ pain and aesthetics subscale scores had in general very low correlations with any of the other outcome measures, except for the correlation between the MHQ pain score and the SODA pain score and the MHQ aesthetics score and the SODA score.

Table 5 shows that in the intervention group the hand function of patients improved significantly directly after a 12 week multidisciplinary treatment programme. For the MHQ subscales overall hand function, activities of daily living, work performance, satisfaction, as well as the MHQ total score the improvement reached statistical significance after 12 week follow up. Regarding the other measures of (hand) function the improvements of the HAQ, HAMIS and grip strength were statistically significant.

The MHQ total score as well as the MHQ subscales activities of daily living, work performance, satisfaction demonstrated a moderate SRM, with values ranging between -0.68 and -0.74. As for the other measures of hand function, the SRM of the HAMIS (0.71) and grip strength (-0.74) were also moderate. The ES of the MHQ subscales work (-0.63) and satisfaction (0.55) were moderate. For all other measures, effect sizes were small.

Regarding the RR 8 patients indicated an improved hand function, 11 rated their hand function as unchanged, and 1 a worsened hand function. Of five patients a rating was missing. The MHQ subscales work (-1.26), aesthetics (-0.83), an SODA (0.91) demonstrated a good responsiveness ratio, the MHQ total score (-0.74) and HAMIS (0.75) a moderate responsiveness ratio (30). None of the measures of (hand) function showed a responsiveness ratio above the strict cut off point of 1.96 (28).

Table 6 shows the difference in mean change scores and the pooled ES of the MHQ and subscales as well as other measures of (hand) function between the intervention and control groups. Except for the subscale scores pain and aesthetics (0.09 and 0.29, respectively), the pooled ES of the MHQ total and subscale scores was moderate to good (ranging between 0.56 and 0.86), with only the pooled ES for grip strength being larger (0.97).

Table 5. Baseline, 12 week follow-up scores and measures of responsiveness of MHQ subscales, MHQ total score and other hand function indices of 25 systemic sclerosis patients completing a multidisciplinary team care programme

	baseline	12 week follow up	Change baseline tot 12 week (95% CI)	P value†	Standardized Response Mean ‡	Effect Size‡	Responsiveness ratio‡#
MHQ Function	58.1 (18.1)	62.8 (15.6)	4.7 (0.5, 8.9)	0.030	-0.47	-0.26	-0.10
MHQ Activities of daily living	75.1 (20.8)	82.5 (17.4)	7.4 (3.0, 11.8)	0.002	-0.70	-0.36	-0.19
MHQ Work	62.0 (21.2)	75.4 (24.3)	13.4 (5.4, 21.4)	0.002	-0.71	-0.63	-1.26
MHQ Pain	38.1 (29.3)	32.8 (29.8)	-5.2 (-13.4, 2.9)	0.198	0.27	0.18	-0
MHQ Aesthetics	66.8 (19.3)	71.0 (21.8)	4.2 (-4.8, 13.2)	0.349	-0.20	-0.22	-0.83
MHQ Satisfaction	54.0 (22.3)	66.3 (23.0)	12.3 (4.7, 19.9)	0.003	-0.68	-0.55	-0.51
MHQ Total score	59.0 (12.5)	65.1 (11.5)	6.1 (2.6, 9.6)	0.001	-0.74	-0.49	-0.74
HAQ (0-3) (SD)	0.89 (0.66)	0.72 (0.6)	-0.18 (-0.36, -0)	0.049	0.44	0.26	0.32
HAMIS mean (0-27), (SD)	7.4 (5.5)	5.9 (4.9)	-1.2 (-2.2, -0.3)	0.014	0.71	0.27	0.75
Grip strength right (J), (SD)	26.1 (14.1)	29.2 (12.7)	2.8 (0.8, 4.6)	0.008	-0.74	-0.22	-0.35
Pinch grip right (N), (SD)	4.4 (2.3)	4.4 (1.9)	-0.2 (-0.8, 0.5)	0.602	0	0	0.46
SODA	81.1 (14.5)	84.6 (12.1)	5.0 (-1.5, 11.5)	0.087	-0.27	-0.24	-0.91
SODA pain	1.1 (2.2)	0.7 (1.5)	-0.6 (-1.6, 0.4)	0.236	0.2	0.18	0.19

MHQ=Michigan Hand Questionnaire; HAQ=Health Assessment Questionnaire; HAMIS= Hand Mobility in Scleroderma; SODA=Sequential occupational dexterity assessment; †P value of t test, significance set at P< 0.05. ‡ For all measures a positive change score (post-treatment mean – pre-treatment mean) means improvement, except for the MHQ pain score, the SODA pain score and HAMIS score where a negative change score means improvement. # The Responsiveness ratio could only be computed for 20/25 patients as in 5 patients no general rating of treatment effect was available.

Table 6. Effect size (ES) for difference in various measures of hand function in patients with SSc between intervention and control groups.

	Difference (95% confidence interval) between mean change in treatment (n=28) and control group (n=25)	Pooled ES
MHQ Function	5.9 (0.3, 11.5)	0.61
MHQ Activities of daily living	8.1 (1.9, 14.3)	0.74
MHQ Work performance	14.1 (3.7, 24.5)	0.77
MHQ Pain	-1.5 (-12.0, 8.9)	-0.09
MHQ Aesthetics	5.8 (-6.4, 18.0)	0.29
MHQ Satisfaction	9.7 (-0.4, 19.9)	0.56
MHQ Total score	7.0 (2.5, 11.6)	0.86
HAQ (0-3) (SD)	-0.30 (-0.53, -0.08)	0.82
HAMIS mean (0-27), (SD)	-1.0 (-2.3, 0.3)	0.47
Grip strength right (J), (SD)	4.49 (2.0, 7.0)	0.97
Pinch grip right (N), (SD)	-0.04 (-0.84, 0.75)	0.03
SODA	3.6 (-5.4, 12.6)	0.33
SODA pain	1.13 (-2.6, 0.3)	0.60

MHQ= Michigan Hand Questionnaire; HAQ=Health Assessment Questionnaire; HAMIS= Hand Mobility In Scleroderma; SODA= Sequential Occupational Dexterity Assessment;

Discussion

In this study, in patients with SSc completing a 12-week multidisciplinary team care programme including a hand function treatment module, the MHQ and most of its subscales proved to have a good internal consistency and adequate convergent validity. The MHQ total score was found to be a responsive measure of hand function in patients with SSc, with in general more favourable results in detecting changes over time and discriminating between a treatment and a control condition than all other measures of (hand) function.

The MHQ captures important aspects of hand function in SSc such as aesthetics, satisfaction with hand function and pain that are not addressed by other hand function tests .So far, data on the internal consistency, validity and responsiveness of the MHQ in SSc are scarce. No other studies have reported on the internal consistency in patients with SSc, with the results of the present study being quite favourable. Preliminary results of its validity have been presented in a cohort of 94 patients with SSc (17). In that study the correlations between the MHQ and its subscales on the one side and hand features such as skin score, digital ulcers and tendon involvement on the other side were assessed. Significant Spearman rank correlation coefficients were seen between the MHQ and tendon involvement, whereas associations with skin score and digital ulcers were weak. In our study the correlation between the MHQ and the MRSS was somewhat higher and the presence of digital ulcers or tendon friction rubs was not assessed. However, the present study showed a moderate correlation of the MHQ and its subscales with the HAQ, and to a lower extent with the HAMIS, SODA and SODA Pain scores. Overall, correlations between the MHQ and grip and pinch grip were weak, except for the association of the MHQ subscale activities of daily living with grip and pinch strength.

Concerning the responsiveness of the MHQ, its performance was moderate to good. In comparison with the other measures of hand function, the ability of the MHQ and its subscales to detect changes over time or a difference between the intervention and control conditions was in the same range or better than that of other measures of (hand) function. The modest sensitivity to change may reflect a limited effect of the intervention. The lack of effect could be due to the mild disability hand disability of the patients participating in this study as well as moderate intensity of the hand treatment programme as compared tot other programmes (35) .

The responsiveness of the MHQ subscale pain to detect changes over time was very low, and in line with the results of the SODA pain. Concerning the difference between the intervention and control group however, the pooled ES of the SODA pain was considerably larger than that of the MHQ subscale pain. Inconsistencies between the MHQ subscale pain and the SODA pain score can probably be explained by the different

way pain is evaluated. In the SODA pain score patients indicate pain with standardized uni/bilateral ADL tasks, whereas the MHQ evaluates general pain using four out of five questions.

Concerning the clinimetric properties of the MHQ in other rheumatic diseases with hand involvement, the MHQ demonstrated comparable measures of construct validity but proved to be less responsive to change (18;36). This may also be due to the mild disability hand disability of the patients participating in the present study as well as moderate intensity of the hand treatment program as compared to other interventions (18).

A limitation of this study is the fact that no direct comparison was made with the Cochin Hand Function Scale (CHFS), a self-administered questionnaire that is frequently used in hand function assessment (4). The CHFS compromises 18 hand activity questions with 6 levels of answers with more detailed focus on activity of daily living, but lacks questions concerning pain, satisfaction and aesthetics. For this reason the MHQ and CHFS may complement each other well.

In conclusion, the results of the present study indicate that the MHQ is a valuable instrument for the measurement of hand function in patients with SSc. As the present study concerned a selected group of patients with SSc, the results need to be confirmed in a larger population.

CHAPTER 6

Work status and its determinants among patients with Systemic Sclerosis; a systematic review.

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A.A. Schouffoer, J.W. Schoones, C.B. Terwee, T.P.M. Vliet Vlieland.

Abstract

Objective:
To describe work status and factors associated with work disability (WD) in patients with Systemic Sclerosis (SSc).

Methods:
A systematic search strategy in various electronic databases from 1990 to 2011 was performed. All clinical studies concerning SSc patients containing quantitative information on work status and/or factors associated WD were selected. Extracted were: study-characteristics, data on work status and/or factors associated with WD. The methodological quality was evaluated in three quality aspects (selection bias, information bias and statistical analysis bias). A best evidence synthesis was employed to analyze the association between potential determinants and WD.

Results:
Twelve studies, described in 13 papers, including 2.758 SSc patients were selected. The methodological quality of one study was high. Employment rates varied between 11% and 82% after an average disease duration ranging from 2.5 to 14 years. There was moderate evidence for an association between more functional disability, more disease specific symptoms and worse quality of life on one side and presence of WD on the other. There was moderate evidence for the absence of an association between WD and age, sex and disease subset. Inconsistent evidence was seen for an association between WD and education and disease duration.

Conclusion:
WD is a major consequence of the disease in patients with SSc and is associated with more functional disability, more disease specific symptoms and worse quality of life. This emphasizes the need for research into interventions to prevent or reduce WD in patients with SSc, especially in those with a worse health status.

Introduction

Systemic Sclerosis (SSc) is a chronic, multi-system disease with unknown etiology, characterized by skin sclerosis, vasculopathy and complications of internal organs (1). Despite the variable course of symptoms the associated morbidity is considered to be substantial. Two major subsets are defined: limited cutaneous systemic sclerosis (lcSSc) and diffuse systemic sclerosis (dSSc) (2). In lcSSc, Raynaud's phenomenon and a slowly progressive thickening of the skin of distal extremities may have been present for years before patients seek medical attention. DcSSc has a rapid onset of skin thickening at proximal sites and involvement of internal organs. SSc disease manifestations include pain, fatigue and malaise, disabling digital tip ischemia, limited range of joint motion and flexion contractures, calcinosis, organ fibrosis and pulmonary arterial hypertension (3). Emotional distress is common in SSc, including depression, low self-esteem, concerns with physical appearance, and feelings of uncertainty about the future (4;5). Although medical treatment in SSc may alleviate symptoms, prevent complications or influence inflammation, so far a cure is not available.
Using the International Classification of Functioning, Disability and Health to describe patients' health status (6), considerable disability (impairments of body functions and structures, activity limitations and participation restrictions) has been demonstrated in SSc patients (7-9). Work disability in rheumatic conditions is usually defined as complete or partial work cessation due to the disease prior to the age of retirement (10), however in some studies a broader definition is used, also concerning any restriction in the work status, such as absenteeism or sick leave, or any reduction in productivity while present at work (so called presenteeism). Apart from work disability, productivity loss is also used as an umbrella term for work cessation, sick leave/absenteeism or reduction in productivity while present at work.
The impact of the disease on participation in particular on work status, in other inflammatory rheumatic conditions is overall well-documented (11;12). The results of recent studies in SSc on this subject all point into the direction of substantial work disability (13-15). This is unfavorable as it was also found that in SSc patients greater work ability was associated with more satisfaction with occupations in general and better well-being (16). In addition, a number of recent studies aimed to identify risk factors for work disability in SSc patients (17;18). These studies found that lower educational level, less social support, poor functional ability and longer disease duration were associated with work disability.
The growing number of publications on work status in SSc underlines the importance of the subject. So far, the literature has not been summarized by means of a systematic review. Therefore, the aim of the present study was to perform a systematic literature review on work status in SSc patients defined as the ability or inability to perform a paid job. More specific, we describe the prevalence of work disability in SSc as compared

with other inflammatory disease as well as the risk factors for work disability. For the latter purpose, medical and rehabilitative interventions were included as potential determinants of work status in SSc.

Methods

Search strategy.
In cooperation with a trained librarian (JS), a search strategy was composed. The following databases were searched: PubMed, EMBASE (OVID version), Web of Science, COCHRANE Library, CINAHL (EbscoHost-version), PsycINFO (EbscoHost-version), Academic Search Premier and ScienceDirect. The search strategy consisted of the AND combination of two main concepts: Work Disability, and Systemic Sclerosis. For the different concepts, all relevant keyword variations were used, not only keyword variations in the controlled vocabularies of the various databases, but the free text word variations of these concepts as well (Appendix 1).
The search strategy was optimized for all consulted databases, taking into account the differences of the various controlled vocabularies as well as the differences of database-specific technical variations (e.g., the use of quotation marks). The search was performed on the 23rd of May, 2011.

Data collection and analysis.
Five steps in the selection and data collection were defined. All steps were performed by two of the authors independently (AS and TPMVV) and any discrepancies were resolved by consensus.

Step 1: Screening of titles and abstracts. First, duplicates were removed. Subsequently, titles and/or abstracts which were not directly related to a full-text paper were taken out.
For screening of the remaining titles and abstracts the following criteria were used: (i) the publication concerned a clinical study; (ii) the study population consisted of subjects with a diagnosis SSc according to the criteria as set by the American College of Rheumatology criteria and/or Leroy & Medsger criteria (2); studies with a mixed patient population were included if data on SSc patients were available separately; (iii) the publication contained information on work status or derivates.

Step 2: Selection of full-text papers. Titles and abstracts identified as potentially eligible were selected for full-article review.
The following selection criteria were used for the full text papers:
(i) Studies contained quantitative information on work status including: working full-time, working part-time, number of hours working, early retirement, unemployment, absenteeism and/or presenteeism, permanent work disability (job loss and/or partial or full disability pension).
(ii) The study concerned quantitative information on predictors for work status as defined under (i), including the potential impact of interventions such as medical treatment or vocational rehabilitation.
(iii) The article was written in the English language.

Step 3: Data extraction. From the included full text papers the following study characteristics were systematically extracted: author, year of publication, country where the study was conducted, study design (cross-sectional or longitudinal), number of SSc patients, patient recruitment or selection criteria, average age (years), number of female patients (%), average disease duration (years), number of patients with a dcSSc (%). Regarding the outcomes of studies in terms of work status, the definition(s) of work status and associated outcome measures were recorded.
If a study included an analysis of determinants of work status, the following data were extracted: dependent variable (any outcome measure(s) related to work status) and the potential determinants examined, categorized into: i) sociodemographic characteristics (age, sex, educational level or other); ii) disease characteristics (SSc subset, disease duration, functional ability, disease specific symptoms, quality of life or other disease characteristics), iii) work characteristics; and iv) other.

Step 4: Assessment of methodological quality
To assess the quality of the included studies, a quality checklist (Appendix 2) was developed, based on items described in a review of tools for quality assessment (19) and on a review on the quality of prognostic studies in systematic reviews (20). Two authors independently assessed the quality of each study by scoring 23 items (Appendix 2), divided into three categories: i) selection bias (items 1-6); ii) information bias (items 7-18); and iii) statistical analysis of potential determinants of work status (items 19-23). Bias was considered present if the majority of the items within a category pointed into this direction. The quality of the study was rated as high if there was no evidence for selection bias, information bias or analyses bias. The quality of the study was rated as moderate if there was evidence of bias in one out of two categories in descriptive studies (statistical analysis of factors associated with work disability not applicable), or two out of three categories in studies comprising an analysis of associations between various factors on the one side and work status on the other hand. The quality of the study was rated as low if there was evidence of bias in both two categories in descriptive studies and all three categories in the other studies.

Step 5: Best evidence synthesis
A best evidence synthesis was applied in order to synthesize the results of the studies,

while taking into account the number of studies, the methodological quality of the studies, and the consistency of the results. This rating system (Appendix 3) was based on levels of evidence as described by review groups from the Cochrane Collaboration.

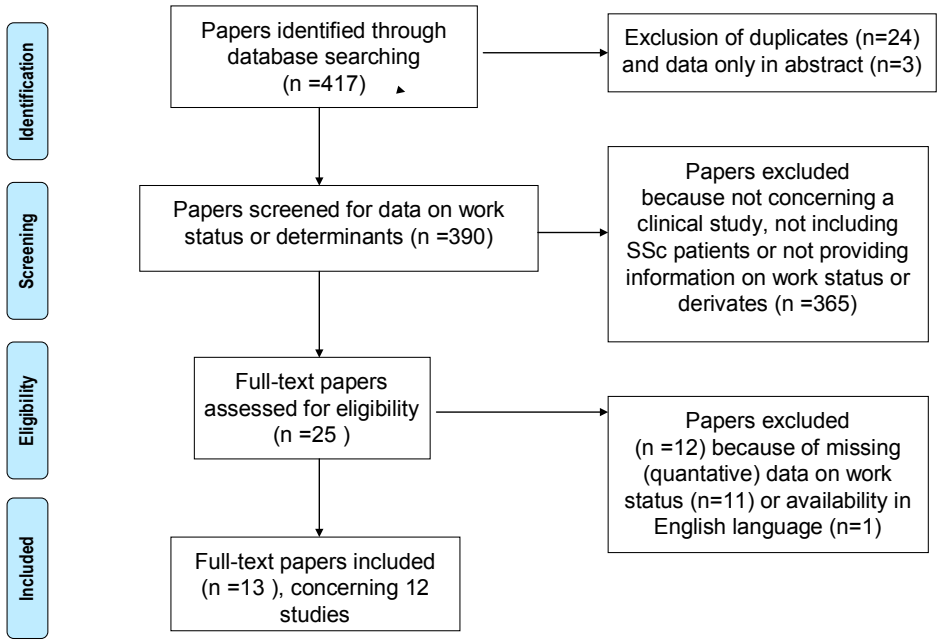

Figure 1

Results

Selection of papers

The bibliographic databases yielded 417 references in total (Figure 1). Twenty-four duplicates were excluded, in addition three titles were excluded because data were presented only in abstract form.

The first screening of the remaining 390 titles and abstracts resulted in exclusion of 365 abstracts because these did not concern a clinical study, did not include SSc patients or provided no information on work status or derivates. Full text screening of 25 remaining potentially eligible papers resulted in exclusion of twelve papers because (quantative) data on work status were missing (n=11) or they were not written in English (n=1). Finally, thirteen papers were selected for inclusion (13-18;21-27). In two included papers the same inclusion criteria were used, a similar number of patients was included and similar demographic characteristics were reported (16;27). Therefore, these two

papers were considered as one study, resulting in a final number of studies of twelve. For data extraction and the assessment of quality the information of both studies was combined.

Study characteristics

The characteristics of the selected studies are presented in Table 1. The studies were all performed in Europe or North America. Eleven of the 12 studies had a cross-sectional design, whereas one study had a prospective design with a mean follow-up of 4.4 years (18). Eight out of twelve studies comprised an analysis of associations between various factors on the one side and work status on the other hand.

Patients were recruited through department registers of rheumatology centers/ outpatient clinics (14;16;21;22;27), multi-center registers (17;23), a national registry (24) or using various recruitment strategies including public announcements or advertisements (13;15;18;25). The numbers of participants

included in the studies varied from 36 to 802, the average ages from 47 to 58 years, the proportions being female from 82.8 to 100%, the proportions with diffuse subtype SSc from 0 to 59% and the mean/median disease duration from 2.5 to 14 years. Some of the studies employed an inclusion criterion regarding the maximum age of patients (16;21;24;26;27), in order to only include patients of working age. In addition, none of the studies included only patients who had a paid job at the time of diagnosis.

Methodological quality

Table 2 summarizes the result of the quality assessment. Four studies (22;23;25;26) were only descriptive with respect to work status (maximum 2 points) whereas 8 studies (13-18;21;24;27) concerned an analysis of factors associated with work status (maximum 3 points). The methodological quality was rated as high in two studies (17;26), moderate in nine (13-16;18;23-25;27), and low in one study (22).

Table 1: Characteristics and reported outcomes of twelve studies on work status in patients with Systemic Sclerosis

Study (ref nr) (country year)	*Study design*	*No. of patients*	*Patient recruitment and selection*	*Age; mean (years)*	*Female; No (%)*	*Mean disease duration, years (SD)*	*DcSSc; No (%)*	*Definition of work status*	*Results*
Moser (25) USA 1993	Cross sectional	94	Referrals from scleroderma clinics, private practice physicians and announcements in newsletters	55 (SD 12)	83 (88.3)	8 (SD 7)	n.a.	Working part-time or full-time, being a homemaker, being retired, being disabled	Working part- or full-time outside the house 23/94 (24.5%) Homemaker 17/94 (18.1%) Retired 27/94 (28.7%) Disabled 23/94 (24.5%)
Mau (24) Germany 2005	Cross sectional	802	National registry, age 20-59 yrs	47 (SD 10)	667 (83%)	361 (48%) ≤ 5 yrs, 212 (28%) 6-10 yrs, 186 (25%) >10 yrs	n.a.	Gainful employment; Standardized Employment Ratio (SER)=observed/ expected employment (95% CI)	SER Women: New Federal States 0.70 (0.52-0.92) Old Federal States 0.77 (0.67-0.87); SER for part time employment: 1.06 (0.82-1.35) SER Men: New Federal States: 0.90 (0.51-1.46) Old Federal states: Men 0.84 (0.66-1.05),)
Sandqvist (26) Sweden 2005	Cross sectional	36	Women aged 20-60 years with limited SSc living in Southern the region of Sweden	Median 52 (range 24-59)	100%	Median 9 (range2-44)	0	Working between 50-100% of fulltime, combining work with sick pension, temporarily sick, full sick pension	16/36 (44.4%) working between 50-100% 3/36 (8%) temporarily sick 12/36 (33.3%) partial sick pension 5/36 (14%) full time sick pension
Sandqvist (16, 27) Sweden 2008	Cross sectional	44		Median 52 (range 24-60)	100%	Median 8 (range 2-44)	0	Partial sick leave(20-50% of ordinary working day), full time sick leave or disability pension	21/44 (48%) working full time; paid work 6.25 hour/day (range 0-11), 15/44 (34%) partial sick leave 8/44 (18%) full time sick leave or full time disability pension
Ouimet (14) Canada 2008	Cross sectional	61	Outpatient clinic; SSc patients who were retired or had never worked were excluded	52 (SD 1.18)	85.2%	11.02 (SD 1.22)	26 (43%)	Working, working in the home (not work disabled) or having stopped working due to illness (work disabled).	27/61 (44%) working or working in the home" 34/61 (56%) patients with work disability
Bernatsky (23) Canada 2009	Cross sectional	457	National scleroderma registry	55.1 (SD 12.1)	401 (87.7%)	10.5 (SD 8.6)	185 (40%)	Lost productivity based on self reported days that the patient was unable to work (market work and unpaid labor)	Average cost per patient in 2007 Canadian dollars: Paid labor lost productivity 5.345 (4.598, 6.092) Unpaid labor lost productivity 8.070 (7.167, 8.973)
Hudson (17) Canada 2009	Cross sectional	643	National scleroderma registry, age > 18 years	50.2 (SD 8.2) in work disabled patients (n=133); 48.4 (SD 9.4) in working patients (n=232)	84% in work disabled patients (n=133); 83% in working patients (n=232)	11.0 (8.6) in work disabled patients (n=133); 9.0 (7.7) in working patients (n=232)	59 % in work disabled patients (n=133); 42% in working patients (n=232)	Currently working,part-time, full-time or self-employed; Currently retired, student, disabled, on sick leave, unemployed, home maker or other	232/643 (36%) working 133/643 (21%) work disabled Remainder > 65 years, retired, students, homemakers or unemployed
Nguyen (13) France 2010	Cross sectional	87	SSc patient association and hospitalized patients	48.6 (SD 8.5)	72 (82.8%)	8.1 (SD 6.4)	30 (34.5%)	Current full-time sick leave status (yes/no); presence and duration of work disability pension; work-time duration (part-time or full-time); Changes of working time; Occupational changes	34/87 (39%) working (24/87 (28%) fulltime, 10/34 (11%) parttime); 15/34 (44%) changed working-time after the diagnosis 53/87 (61%) on full-time sick leave 31/87 (36%) had a disability pension 27/87 (31%) experienced occupational changes after diagnosis.
Minier (22) Hungary 2010 june	Cross sectional	80	Tertiary care centre, SSc patients ≥ 18 years	57.4 (SD 9.6)	72 (90%)	6.2 (SD 6.6)	20 (25%)	Working (full-time, part-time); sick leave ; disability pension; retired	9/80 (11.3%) working (7(9%) full time, 2 (2%) part time) 1/80 (1.3%) permanent sick leave 39/80 (48.8 %) disability allowance 32/80 (40%) retired

Study (ref nr) (country year)	*Study design*	*No. of patients*	*Patient recruitment and selection*	*Age; mean (years)*	*Female; No (%)*	*Mean disease duration, years (SD)*	*DcSSc; No (%)*	*Definition of work status*	*Results*
Sandqvist (21) Sweden 2010	Cross sectional	57	Patients aged 20-65 years with SSc living in Southern the region of Sweden	Median 58 (IQR 47-62)	53 (93%)	Median 14 (IQR 9-19)	10 (18%)	Work Ability Index (WAI; range 7-49) ; Employment status: Working without sickness benefit, partially on sick leave, fulltime sick leave or disability pension	Median WAI score 32 (range 16.8-37)& 13/57 (23%) good or excellent WAI (>36) 15/57 (26%) less good WAI (28-36) 20/57 (35%) poor WAI (<28) 16/57 (28%) working without sickness benefit 20/57 (35%) partial sick leave 21/57 (37%) full time sick leave
Bérezné (15) France 2011	Cross-sectional	189 (113 patients 18-61 years)	SSc patient association and hospitalized patients	54.1 (SD 13.3)	164 (86.8)	9.3 (SD 8.4)	78 /179 (43.6%)	Employed, retired, home-maker, student, on sick leave, or looking for a job	67/113 (59.3%) employed (42 (37.2%) fulltime, 23 (20.3%) parttime. 27/113 (23.9%) on sick leave at time of inclusion, duration of sick leave 3.4 weeks (SD 4.6) 7/113 (6.2%) retired early due to SSc. 6/113 (31.8%) full disability pension
Sharif (18) Texas USA 2011	Pros-pective	284	≥ 18 years, disease onset < 5 years at enrolment, defined ethnicity; 3 hospitals	48.7 (SD 13.2)	237 (83.5%)	Mean 2.5 (SD 1.6)	162 (57.0%)	Work disabled, working and retired or home-maker	Baseline: 131 (46.1%) non-work disabled (group A) 124 (43.7) work disabled (group B) 29 (10.2) retired or home maker (group C) Follow-up group A (after 3.9 (SD 3.6 years for whole group) 96/131 (73.3%) still working 35 (26.7%) became work disabled

SD= standard deviation; DcSSc= diffuse cutaneous Systemic Sclerosis; SD=Standard Deviation; IQR= Interquartile Range; n.a.= not applicable; SER= Standardized Employment Ratios

Table 2: Quality assessment of 12 included studies concerning 13 papers

	selection bias present [§]	information bias present [§]	statistical analysis bias present [§]	Total score	Level of quality*
Descriptive studies					
Minier (22)	1	1	N.a.	2/2	L
Bernatsky (23)	1	0	N.a.[@]	1/2	M
Sandqvist (26)	0	0	N.a.	0/2	H
Moser (25)	1	0	N.a.[@]	1/2	M
Studies concerning an analysis of factors associated with work ability					
Ouimet (14)	1	0	0	1/3	M
Mau (24)	1	0	0	1/3	M
Hudson (17)	0	0	0	0/3	H
Sandqvist (16, 27)	0	0	1	1/3	M
Berezne (15)	1	0	0	1/3	M
Nguyen (13)	1	0	0	1/3	M
Sharif (18)	1	0	0	1/3	M
Sandqvist (21)	0	0	1	1/3	M

[§] 1=risk of bias; 0= no risk of bias present. *H= high quality; no evidence for selection bias, information bias or analyses bias. M= moderate quality: in one or two quality aspects evidence for risk of bias. L= low quality: all evidence for risk of bias; [@] multivariate analysis not concerning a work ability outcome

Work status in SSc

Measurement methods

Table 1 shows the measurement methods for work status of the 12 studies. One study used a standardized method using data from the general population (24). In that study standardized Employment Ratios (SER) were used, defined as the ratios of observed and expected numbers of patients with gainful employment. One study used the Work Ability Index (WAI), a combined measure of absenteeism, presenteeism, and work ability in relation to demands of the work, psychological resources, number of diagnosed diseases and estimation of own impairment and prognosis (21). One study reported work status in terms of productivity, defined as the number of self-reported days that the patient was unable to work (market work and unpaid labor) (23). The other included studies used various operationalizations of work status; mostly proportions of patients who were working, stopped working, were on sick leave or the combination of both (13-18;22;25-27)

In some studies, information on work status was gathered as part of other research questions and analyses, including cost-of-illness (22;23), psychosocial adjustment (25) and time use and satisfaction with occupation (27).

Work ability outcomes

In the one study which used work ability rates that were standardized using data from the general population SERs of 0.70 (95% CI 0.52-0.92) and 0.77 (95% CI 0.67-0.87) were observed in women with SSc in the new and old federal states of Germany, respectively. The SER of men with SSc also indicated work disability; however these results did not reach statistical significance.

Regarding the outcomes in terms of proportions of patients being employed, Table 1 shows that all but one (23) study provided information in this way. The highest reported percentage was 82% in a Swedish study with 44 female patients with limited SSc and a median disease duration of 8 years (16). The lowest reported proportion of patients being employed (either part time or full time) was 11.3%, observed in a cross-sectional study with 80 patients with SSc with a mean age 57.4 years and mean disease duration of 6.2 years, of whom 90% were female (22). Direct comparisons of proportions of patients working need to be interpreted with caution as the selection of patients and disease duration varied widely among studies.

With respect to sick leave rates six studies (13;15;16;22;26;27) reported proportions of patients being on partial or full-time sick leave in mostly cross sectional design, with the rates for full time sick leave ranging between 1.3 and 61% and part time sick leave ranging between 8% and 35% in patients with a disease duration varying from 6.2 to 14 years. Two studies provided information on work status in terms of productivity; Berezne et al (15) reported an estimated SSc related decreased work productivity of 3.4 hours/month (±3.8). Bernatsky et al (23) estimated a lost productivity of paid labor of 5345 Canadian dollars per patient per year.

Work status in patients with SSc as compared to other rheumatic conditions

Two studies included a direct comparison of work disability rates in patients with SSc as compared to other rheumatic diseases (14;24). In one study, more work disability was seen in SSc patients as compared to an age and sex matched cohort of Rheumatoid Arthritis (RA) patients ; 55.7 % versus 34.6 % (p=0.009) after a mean disease duration of 11 versus 12 year. (14). In another study (24) the SER was 0.77 in patients with SSc, 0.78 in rheumatoid arthritis (RA), 0.94 in ankylosing spondylitis, 0.92 in psoriatic arthritis, 0.81 in Systemic Lupus Erythematosus and 0.76 in polyangiitis (Wegener's) with the SERs being significantly different from the general population for all these patient groups.

Determinants of work status

Table 3 shows the results of the 8 studies examining determinants of work status (13-18;21;24). In case of both univariate and multivariate analyses only the results of the multivariate analyses were presented. Overall, there was a large heterogeneity in the included potential determinants of work status, the definitions of the work status, the possible confounders as well as the used analyses.

Table 3 shows that there is moderate evidence for an association between more functional disability, decreased quality of life, more disease specific symptoms and more work disability. Also, moderate evidence was found for the absence of an association between age, sex and disease subset and work disability. Results concerning other predictors of work disability, including educational level and other demographic or job characteristics and disease duration, were not consistent.

Discussion

This systematic review on work status and its determinants in SSc included 12 studies. Although the definitions of work status varied widely among studies, the results indicate substantial work disability. Moderate evidence was found for an association between functional disability, quality of life and disease specific symptoms and work disability. Also, moderate evidence was found for the absence of an association between age, sex and disease subset and work disability. Results concerning other predictors of work disability were not consistent.

With respect to the extent of work disability, the majority of studies reported outcomes in terms of proportions of patients working as opposed to proportions of patients who stopped working or were on sick leave or the combination of both. In the included studies, the proportions of patients working varied from 11% (22) to 82% (16), the highest number concerning patients with limited SSc. Only one study (24) used standardized employment rates, demonstrating significantly reduced participation in patients with SSc.

Most studies included in this review had a cross sectional design and used employment rates and permanent work disability as outcome measures, while data on sick leave or presenteeism were presented in relatively few (15;16;21;23). This is unfortunate as it was demonstrated in other inflammatory disease that sick leave is an independent risk factor for job loss (28). Moreover, information on any degree of productivity loss is essential in establishing the economic impact of SSc.

Comparisons of work disability rates among studies are hampered by differences in patient populations with respect to disease duration and severity, age and employment rate prior to the established diagnosis as well as definitions of work status. Comparison between studies performed in the various countries is further limited by differences in populations, differences in work force participation in female and general population and social security systems.

To facilitate the interpretation and comparison of work status rates within and among patient groups, standardized assessments of work disability are recommended, including consensus on the definitions of the various aspects of work status as well as standardization using data from the general population

In addition it is questionable whether cross-sectional studies are suitable to describe

the impact of SSc on work disability. Preferably, work ability should be regarded as a continuum, in which periods of decreased work productivity while present at work, temporary absence or sick leave may precede or follow periods during which patients are not working at all, due to official unemployment, work disability, early retirement and/or voluntary
stopping work (29). Prospective cohort studies are needed to describe productivity gains and losses over time in this continuum model, taking factors such as age, sex, education and other socio-demographic variables, as well as an appropriate description of jobs and job demands, into account.

As for the determinants of work disability, moderate evidence was found for an association between functional disability, quality of life and disease specific symptoms and work disability. Many factors may influence work disability; personal factors (personality, coping mechanisms, education), environmental influences (financial resources, social security systems), work characteristics (physical demanding or not, flexibility in working hours, aids and other occupational interventions), pharmacological or non-pharmacological treatment and vocational therapy. Sandqvist (16) observed less sick leave in patients with less physically demanding work. As for work dependent influences on work disability, no other determinants were evaluated, nor the effect of any kind of medical or rehabilitative treatment on work disability. Given the general observation that work disability in SSc is substantial, more research targeted at potentially modifiable factors (e.g. disease severity by optimizing medical treatment and job demands by vocational rehabilitation) is urgently needed.

The question remains how the severity of work disability in SSc compares to that in other rheumatic conditions. Comparisons with work disability rates in patients with other rheumatic conditions reported in other individual studies or reviews are difficult to make, as patient populations may differ largely with respect to age, sex, and disease duration and the definitions of outcomes related to work status also vary. However, two studies included in this review included one or more populations of patients with other inflammatory rheumatic conditions, allowing a direct comparison. In one study it appeared that work disability in SSc was more frequent than in RA then SSc (14), whereas in another study the relative risk of higher/lower SER was comparable with RA (24).

Limitations of this review include the fact that statistical pooling of data was not applied due to the heterogeneity of data. A best evidence synthesis was employed, which accounted for the methodological quality of the studies. Moreover, this systematic review focused on paid labor only. The feminine predominance and older age in SSc patients warrants more research on the impact of the disease on unpaid labor. Future studies on work disability should therefore distinguish between paid and non paid work in order to establish the full impact of SSc on any kind of productivity.

Although the differences in outcomes and definitions of work disability make generalization of results challenging, this review shows that work disability in SSc is substantial. The validity of data on work disability and its predictors could be improved by prospective studies with clearly defined patient characteristics as well as end points for all dimensions of work productivity loss. An important question remains if a patient's risk of permanent work disability can be diminished. Much knowledge could be gained if work status was used as an outcome measure in trials concerning pharmacological or non-pharmacological treatment. In other rheumatic disease, effectiveness of biological therapy (30) and vocational therapy on prevention of work disability (31) was demonstrated, whereas no studies on this subject in SSc patients are known.

Table 3. Results of 8 studies describing factors associated with work disability in patients with Systemic Sclerosis

Study	Methodological quality[a]	Dependent variable (method)	Independent variables							
			Age	**Sex**	**Educational level and other demographic or job characteristics**	**Subset diffuse SSc**	**Disease duration**	**Functional disability**	**(Self perceived) disease specific symptoms**	**Quality of Life and other characteristics of health status**
Mau 2005 (24)	M	Standardized employment ratio (SER)=observed/ expected employment (95% CI)	N.a.	N.a.	Significantly higher SER in Old Federal States (0.90) compared to New Federal states (0.80) in subgroup of women with SSc and >9 years of education[b]	N.a.	Significantly higher SER in subgroups of women with a disease duration 6-10 yrs and > 10 yrs but not in women with disease duration ≤ 5 years.	N.a.	N.a.	N.a.
Sandqvist 2008 (16, 27)	M	Work status - working full time versus - partial sick leave versus - full time sick leave or disability pension	N.s.	N.a.	N.s.	N.a.	N.a.	Greater working ability significantly associated with -Better dexterity -More grip force -Better capacity to perform occupations -More occupations performed -More satisfaction with occupations	Greater working ability significantly associated with -better skin score -less fatigue -less breathlessness	Greater working ability significantly associated with better self-rated health, and greater general life satisfaction
Ouimet 2008 (14)	M	Work disability versus non-work disability	N.s.	N.s.	Significantly less patients who completed high school in work disability versus non-work disability group	N.s.	N.s.	Significantly higher HAQ-DI score in work disabled versus non-work disabled group.	N.s. regarding HAQ pain score	N.a.
Hudson 2009 (17)	H	Work disability (Multivariate) 4 Generalized linear mixed models (number 4 AUC 84.7%)	Unclear	Unclear	Unclear	N.s. (but models 1-3 signicantly more diffuse SSc in work disability)	Longer disease duration significantly associated with work disability	Worse physical function significantly associated with work disability	Worse pain and fatigue significantly associated with work disability except if association with HAQ was added	Worse co-morbidity score significantly associated with work disability
Nguyen 2010 (13)	M	Sick leave versus no sick leave; and work disability pension versus no work disability pension	N.s.	N.s.	N.a.	N.s.	N.s.	Signficantly worse scores regarding global disability (HAQ, Karnofsky performance status), hand disability, mouth disability in patients on sick leave as compared to no sick leave. Significantly worse Karnofsky performance status in patients with work disability pension.	Higher proportion of patients with myalgia in the sick leave group	Worse depression score in sick leave group, no significant differences in quality of life (SF 36) or emotional status (HADS).
Sandqvist 2010 (21)	M	Working Ability Index (WAI); Three subgroups good, less good and bad	N.s..	N.s.	N.s.	N.s.	N.s..	Visual analog scale for hand function better in patients with better WAI scores. Scleroderma Functional Score and satisfaction with activities better in patients with better WAI scores.	Visual analog scales for fatigue, general pain, general stiffness, scars/ulcers better in patients with better WAI scores.	Signficantly greater life satisfaction and empowerment scores in patients with better WAI scores

Study	Methodological quality[a]	Dependent variable (method)	Independent variables							
			Age	**Sex**	**Educational level and other demographic or job characteristics**	**Subset diffuse SSc**	**Disease duration**	**Functional disability**	**(Self perceived) disease specific symptoms**	**Quality of Life and other characteristics of health status**
Berezne 2011 (15)	M	Workers versus work disabled nonworkers	Significantly higher age in work disabled[c]	N.s.	N.a.	N.s.	Significantly longer disease duration in work disabled [c]	Signficantly more global disability (HAQ) and hand disability (CHFS) in work disabled [c]	N.a.	Worse SF-36 physical component scale score in work disabled non- workers [c]
Sharif 2011 (18)	M	Work disability at baseline or development of work disability between baseline and follow up	N.s.[d]	N.s.	Lower level of education and less social support associated with more work disability at baseline; Non-white ethnicity associated with development of work disability at follow up [d]	N.s.	N.s.	N.s. [d]	Higher Medsger Severity Index, higher Fatigue Severity Score significantly associated with more work disability at baseline [d]; Poorer lung function and higher Fatigue Severity Score associated with development of work disability during follow up.	N.a.
Best evidence synthesis			Moderate evidence for lack of association	Moderate evidence for lack of association	Inconsistent evidence	Moderate Evidence for lack of association	Inconsistent evidence	Moderate evidence for positive association	Moderate evidence for positive association	Moderate evidence for positive association

[a]H: high; M: moderate; L: low. [b]In old Federal states unemployment rates were lower than in new Federal states. [c]Multivariate analysis; higher age, higher disease duration, poorer functional ability (HAQ and CHFS) independent risk factors forWD. [d]Multivariate analysis; higher age, not being married, poorer functional ability (HAQ), poorer lung function, more pain and shortness of breath, poorer Quality of Life (SF-36), poorer scores on helplessness and illness behaviour and more comorbidities associated with more WD at baseline in univariate analyses. AUC: area under the ROC curve; CHFS: Cochin Hand Function Scale; HAQ-DI: Health Assessment Questionnaire-Disability Index; SF-36: short form 36; HADS: Hospital Anxiety and Depression Scale depression dimension; NA: not applicable, i.e. not included in the analysis; NS: not significant

Reference List

(1) Clements PJ, Furst DE. Systemic Sclerosis. second, 17-28. 2004.

(2) LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Jr. et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988; 15(2):202-5.

(3) Denton CP, Black CM. Scleroderma--clinical and pathological advances. Best Pract Res Clin Rheumatol 2004; 18(3):271-90.

(4) Haythornthwaite JA, Heinberg LJ, McGuire L. Psychologic factors in scleroderma. Rheum Dis Clin North Am 2003; 29(2):427-39.

(5) Richards HL, Herrick AL, Griffin K, Gwilliam PD, Loukes J, Fortune DG. Systemic sclerosis: patients' perceptions of their condition. Arthritis Rheum 2003; 49(5):689-96.

(6) World Health Organisation (WHO). ICF: International Classification of Functioning, Disability and Health. Geneva, Switserland. 2001. 2001.

(7) Hudson M, Thombs BD, Steele R, Watterson R, Taillefer S, Baron M. Clinical correlates of quality of life in systemic sclerosis measured with the World Health Organization Disability Assessment Schedule II. Arthritis Rheum 2008; 59(2):279-84.

(8) Merkel PA. Measurement of functional status, self-assessment, and psychological well-being in scleroderma. Curr Opin Rheumatol 1998; 10(6):589-94.

(9) Rannou F, Poiraudeau S, Berezne A, Baubet T, Le-Guern V, Cabane J et al. Assessing disability and quality of life in systemic sclerosis: construct validities of the Cochin Hand Function Scale, Health Assessment Questionnaire (HAQ), Systemic Sclerosis HAQ, and Medical Outcomes Study 36-Item Short Form Health Survey. Arthritis Rheum 2007; 57(1):94-102.

(10) Allaire SH. Update on work disability in rheumatic diseases. Curr Opin Rheumatol 2001; 13(2):93-8.

(11) Verstappen SM, Bijlsma JW, Verkleij H, Buskens E, Blaauw AA, ter Borg EJ et al. Overview of work disability in rheumatoid arthritis patients as observed in cross-sectional and longitudinal surveys. Arthritis Rheum 2004; 51(3):488-97.

(12) Boonen A, de VH, van der Heijde D, van der Linden S. Work status and its determinants among patients with ankylosing spondylitis. A systematic literature review. J Rheumatol 2001; 28(5):1056-62.

(13) Nguyen C, Poiraudeau S, Mestre-Stanislas C, Rannou F, Berezne A, Papelard A et al. Employment status and socio-economic burden in systemic sclerosis: a cross-sectional survey. Rheumatology (Oxford) 2010; 49(5):982-9.

(14) Ouimet JM, Pope JE, Gutmanis I, Koval J. Work Disability in Scleroderma is Greater than in Rheumatoid Arthritis and is Predicted by High HAQ Scores. Open Rheumatol J 2008; 2:44-52.

(15) Berezne A, Seror R, Morell-Dubois S, de MM, Fois E, Dzeing-Ella A et al. Impact of systemic sclerosis on occupational and professional activity with attention to patients with digital ulcers. Arthritis Care Res (Hoboken) 2011; 63(2):277-85.
(16) Sandqvist G, Scheja A, Eklund M. Working ability in relation to disease severity, everyday occupations and well-being in women with limited systemic sclerosis. Rheumatology (Oxford) 2008; 47(11):1708-11.
(17) Hudson M, Steele R, Lu Y, Thombs BD, Baron M. Work disability in systemic sclerosis. J Rheumatol 2009; 36(11):2481-6.
(18) Sharif R, Mayes MD, Nicassio PM, Gonzalez EB, Draeger H, McNearney TA et al. Determinants of Work Disability in Patients with Systemic Sclerosis: A Longitudinal Study of the GENISOS Cohort. Semin Arthritis Rheum 2011.
(19) Shamliyan T, Kane RL, Dickinson S. A systematic review of tools used to assess the quality of observational studies that examine incidence or prevalence and risk factors for diseases. J Clin Epidemiol 2010; 63(10):1061-70.
(20) Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006; 144(6):427-37.
(21) Sandqvist G, Scheja A, Hesselstrand R. Pain, fatigue and hand function closely correlated to work ability and employment status in systemic sclerosis. Rheumatology (Oxford) 2010; 49(9):1739-46.
(22) Minier T, Pentek M, Brodszky V, Ecseki A, Karpati K, Polgar A et al. Cost-of-illness of patients with systemic sclerosis in a tertiary care centre. Rheumatology (Oxford) 2010; 49(10):1920-8.
(23) Bernatsky S, Hudson M, Panopalis P, Clarke AE, Pope J, Leclercq S et al. The cost of systemic sclerosis. Arthritis Rheum 2009; 61(1):119-23.
(24) Mau W, Listing J, Huscher D, Zeidler H, Zink A. Employment across chronic inflammatory rheumatic diseases and comparison with the general population. J Rheumatol 2005; 32(4):721-8.
(25) Moser DK, Clements PJ, Brecht ML, Weiner SR. Predictors of psychosocial adjustment in systemic sclerosis. The influence of formal education level, functional ability, hardiness, uncertainty, and social support. Arthritis Rheum 1993; 36(10):1398-405.
(26) Sandqvist G, Akesson A, Eklund M. Daily occupations and well-being in women with limited cutaneous systemic sclerosis. American Journal of Occupational Therapy 2005; 59(4):390-7.
(27) Sandqvist G, Eklund M. Daily occupations--performance, satisfaction and time use, and relations with well-being in women with limited systemic sclerosis. Disabil Rehabil 2008; 30(1):27-35.
(28) de Buck PD, de Bock GH, van DF, van den Hout WB, Vandenbroucke JP, Vliet Vlieland TP. Sick leave as a predictor of job loss in patients with chronic arthritis. Int Arch Occup Environ Health 2006; 80(2):160-70.

(29) Boonen A, Severens JL. The burden of illness of rheumatoid arthritis. Clin Rheumatol 2011; 30 Suppl 1:S3-8. Epub;%2011 Feb 26.:S3-S8.
(30) van den Hout WB, Goekoop-Ruiterman YP, Allaart CF, de Vries-Bouwstra JK, Hazes JM, Kerstens PJ et al. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. Arthritis Rheum 2009; 61(3):291-9.
(31) Vliet Vlieland TPM, de Buck PDM, van den Hout WB. Can anti-TNF agents protect against rheumatoid arthritis associated work disability? International Journal of Clinical Rheumatology 2009;4(5):523-531

Appendix 1 search strategy

Database	Strategy
PubMed	(“Working Disability” OR “work disability” OR “working ability” OR “work ability” OR employment status OR socioeconomic burden OR socio-economic burden OR professional activity OR employment OR Work Capacity Evaluation OR Vocational Rehabilitation OR Absenteeism OR Presenteeism OR “Vocational Guidance”(mesh] OR Workers’ Compensation OR Eligibility Determination OR sick leave OR ((Occupational Medicine OR Occupations OR Occupation OR Occupational OR employment OR work) AND (Disease severity OR Disability Evaluation OR Evaluation OR disability)) OR Cost OR Costs OR Economics OR economics OR “Health care usage” OR “Health care utilization” OR “Health care use” OR “Health care system usage” OR “Health care system utilization” OR “Health care system use”) AND (“Systemic Sclerosis” OR “Scleroderma, Systemic”(mesh] OR “Systemic Scleroderma” OR “Diffuse Scleroderma” OR “Sudden Onset Scleroderma” OR “Progressive Systemic Sclerosis” OR “Progressive Scleroderma” OR “Limited Scleroderma” OR “Limited Systemic Scleroderma” OR “CREST Syndrome” OR “CREST Syndromes” OR “Telangiectasia Syndrome” OR “CRST Syndrome” OR “CRST Syndromes” OR (Calcinosis AND Raynaud AND Sclerodactyly AND Telangiectasia))
EMBASE (OVID-version	1. Focus on Systemic Sclerosis (work disability/ OR “Working Disabilit*”.mp OR “work disabilit*”.mp OR “working abilit*”.mp OR “work abilit*”.mp OR work capacity/ OR exp work/ OR exp occupation/ OR employment status/ OR employment status.mp OR exp employment/ OR socioeconomic*.mp OR exp socioeconomics/ OR socio-economic*.mp OR professional activity.mp OR employment.mp OR Work Capacit*.mp OR vocational rehabilitation/ OR Vocational Rehabilitation.mp OR Absenteeism/ OR Absenteeism.mp OR Presenteeism.mp OR productivity/ OR Vocational Guidance/ OR vocational guidance.mp OR Workers’ Compensation.mp OR workman compensation/ OR Eligibility Determination.mp OR medical leave/ OR sick leave.mp OR medical leave.mp OR ((occupation* OR employment OR work OR worker*) AND (Disease severity OR Disability Evaluation OR Evaluation OR disability)).mp OR Cost.mp OR Costs.mp OR Economic*.mp OR exp economic aspect/ OR health care utilization/ OR “Health care usage”.mp OR “Health care utilization”.mp OR “Health care use”.mp OR “Health care system usage”.mp OR “Health care system utilization”.mp OR “Health care system use”.mp) AND (exp *systemic sclerosis/ OR (“Systemic Scleros*” OR “Systemic Scleroderma*” OR “Diffuse Scleroderma*” OR “Sudden Onset Scleroderma*” OR “Progressive Systemic Scleros*” OR “Progressive Scleroderma*” OR “Limited Scleroderma*” OR “Limited Systemic Scleroderma*” OR “CREST Syndrome*” OR “Telangiectasia Syndrome*” OR “CRST Syndrome*” OR (Calcinosis AND Raynaud AND Sclerodactyly AND Telangiectasia)).ti) 2. No focus on Systemic Sclerosis, and combined with intervention-terms (work disability/ OR “Working Disabilit*”.mp OR “work disabilit*”.mp OR “working abilit*”.mp OR “work abilit*”.mp OR work capacity/ OR exp work/ OR exp occupation/ OR employment status/ OR employment status.mp OR exp employment/ OR socioeconomic*.mp OR exp socioeconomics/ OR socio-economic*.mp OR professional activity.mp OR employment.mp OR Work Capacit*.mp OR vocational rehabilitation/ OR Vocational Rehabilitation.mp OR Absenteeism/ OR Absenteeism.mp OR Presenteeism.mp OR productivity/ OR Vocational Guidance/ OR vocational guidance.mp OR Workers’ Compensation.mp OR workman compensation/ OR Eligibility Determination.mp OR medical leave/ OR sick leave.mp OR medical leave.mp OR ((occupation* OR employment OR work OR worker*) AND (Disease severity OR Disability Evaluation OR Evaluation OR disability)).mp OR Cost.mp OR Costs.mp OR Economic*.mp OR exp economic aspect/ OR health care utilization/ OR “Health care usage”.mp OR “Health care utilization”.mp OR “Health care use”.mp OR “Health care system usage”.mp OR “Health care system utilization”.mp OR “Health care system use”.mp) AND (exp *systemic sclerosis/ OR (“Systemic Scleros*” OR “Systemic Scleroderma*” OR “Diffuse Scleroderma*” OR “Sudden Onset Scleroderma*” OR “Progressive Systemic Scleros*” OR “Progressive Scleroderma*” OR “Limited Scleroderma*” OR “Limited Systemic Scleroderma*” OR “CREST Syndrome*” OR “Telangiectasia Syndrome*” OR “CRST Syndrome*” OR (Calcinosis AND Raynaud AND Sclerodactyly AND Telangiectasia)).mp) AND (exp *drug therapy/ OR intervention*.mp OR medication*.mp OR exp *therapy/ OR exp intervention study/ OR drug*.mp)
Web of Science	1. Focus on Systemic Sclerosis TS=(“working disabilit*” OR “work disabilit*” OR “working abilit*” OR “work abilit*” OR “work capacit*” OR occupation* OR employment* OR socioeconomic* OR socio-economic* OR “professional activity” OR “vocational rehabilitat*” OR Absenteeism OR Presenteeism OR “Vocational Guidance” OR “Workers Compensation” OR “workman compensation” OR “Eligibility Determination” OR “medical leave” OR “sick leave” OR ((occupation* OR employment OR work OR worker*) AND (“Disease severity” OR disabilit*)) OR Cost OR Costs OR Economic* OR “Health care usage” OR “Health care utilization” OR “Health care use” OR “Health care system usage” OR “Health care system utilization” OR “Health care system use”) AND TI=(“systemic scleros*” OR “Systemic Scleroderma*” OR “Diffuse Scleroderma*” OR “Sudden Onset Scleroderma*” OR “Progressive Systemic Scleros*” OR “Progressive Scleroderma*” OR “Limited Scleroderma*” OR “Limited Systemic Scleroderma*” OR “CREST Syndrome*” OR “Telangiectasia Syndrome*” OR “CRST Syndrome*” OR (Calcinosis AND Raynaud AND Sclerodactyly AND Telangiectasia)) 2. Focus on Working disability TI=(“working disabilit*” OR “work disabilit*” OR “working abilit*” OR “work abilit*” OR “work capacit*” OR work OR occupation* OR employment* OR socioeconomic* OR socio-economic* OR “professional activity” OR “vocational rehabilitat*” OR Absenteeism OR Presenteeism OR “Vocational Guidance” OR “Workers Compensation” OR “workman compensation” OR “Eligibility Determination” OR “medical leave” OR “sick leave” OR ((occupation* OR employment OR work OR worker*) AND (“Disease severity” OR disabilit*)) OR Cost OR Costs OR Economic* OR “Health care usage” OR “Health care utilization” OR “Health care use” OR “Health care system usage” OR “Health care system utilization” OR “Health care system use”) AND TS=(“systemic scleros*” OR “Systemic Scleroderma*” OR “Diffuse Scleroderma*” OR “Sudden Onset Scleroderma*” OR “Progressive Systemic Scleros*” OR “Progressive Scleroderma*” OR “Limited Scleroderma*” OR “Limited Systemic Scleroderma*” OR “CREST Syndrome*” OR “Telangiectasia Syndrome*” OR “CRST Syndrome*” OR (Calcinosis AND Raynaud AND Sclerodactyly AND Telangiectasia))
COCHRANE Library CINAHL (EbscoHost-version) PsycINFO (EbscoHost-version) Academic Search Premier	(working disability OR work disability OR working ability OR work ability OR work capacity OR occupation* OR employment* OR socioeconomic* OR socio-economic* OR professional activity OR vocational rehabilitation OR Absenteeism OR Presenteeism OR Vocational Guidance OR Workers Compensation OR workman compensation OR Eligibility Determination OR medical leave OR sick leave OR ((occupation* OR employment OR work OR worker*) AND (Disease severity OR disabilit*)) OR Cost OR Costs OR Economic* OR Health care usage OR Health care utilization OR Health care use OR Health care system usage OR Health care system utilization OR Health care system use) AND (systemic sclerosis OR systemic scleros* OR systemic scleroderma OR Systemic Scleroderma* OR Diffuse Scleroderma* OR Sudden Onset Scleroderma* OR Progressive Systemic Scleros* OR Progressive Scleroderma* OR Limited Scleroderma* OR Limited Systemic Scleroderma* OR CREST Syndrome* OR Telangiectasia Syndrome* OR CRST Syndrome* OR (Calcinosis AND Raynaud AND Sclerodactyly AND Telangiectasia))
ScienceDirect	(working disability OR work disability OR working ability OR work ability OR work capacity OR occupation OR employment OR socioeconomic OR socio-economic OR professional activity OR vocational rehabilitation OR Absenteeism OR Presenteeism OR Vocational Guidance OR Workers Compensation OR workman compensation OR Eligibility Determination OR medical leave OR sick leave OR Cost OR Costs OR Economic OR “Health care usage” OR “Health care utilization” OR “Health care use” OR “Health care system usage” OR “Health care system utilization” OR “Health care system use”) AND TITLE-ABSTR-KEY(systemic sclerosis OR systemic scleroderma OR crest)

Appendix 2: quality checklist

A. Selection bias
Theoretical background 1. Is there a theoretical background for the hypothesis?
Study participation
2. Is the study population clearly described in terms of age, gender, and important SSc characteristics? 3. Is the percentage of eligible subjects who participated in the study (response rate) adequate? (more than 30% is considered inappropriate)
Sampling
4. Are patients who participated in the study similar to eligible non-participants, in terms of age, gender, and important disease characteristics?
Study attrition
5. Is the percentage of subjects available for analysis adequate? (< 30% not too many missing values or loss to follow-up)? 6. Were reasons for loss to follow-up presented and assessed during the study for possible systematic attrition? (subjects that did not finish the study)
B. Information bias
Determinants/correlates measurement
Definition of determinant/correlate 7. Are clear definitions of each determinant and/or correlate provided? 8. Are clear operationalizations of each determinant and/or correlate provided? How is it measured
Measurement of determinants/correlates 9. Are the measurement instruments used for the measurement of the determinants and correlates reliable and valid?
Method and setting of the determinants/correlates 10. Were the measurement approach, time and place of measurement of the determinants and/or correlates standardized or conducted in a way that limits systematically different measurement?
Outcome measurement
Definition of outcome variable(s) 11. Are clear definitions of each outcome variable provided? 12. Are clear operationalizations of each outcome variable provided? How is it measured.
Measurement of outcome variable(s) 13. Are the measurement instruments used for the measurement of the outcome variable(s) reliable and valid?
Method and setting of the outcome variable(s) 14. Were the measurement approach, time and place of measurement of the outcome variable(s) standardized or conducted in a way that limits systematically different measurement?
Study confounding
Definition of potential confounders 15. Are clear definitions of each confounder provided? 16. Are clear operationalizations of each confounder provided?
Measurement of potential confounders 17. Are the measurement instruments used for the measurement of the confounder(s) reliable and valid?
Method and setting of the confounder(s) 18. Were the measurement approach, time and place of measurement of the confounder(s) standardized or conducted in a way that limits systematically different measurement?
C. Statistical analyses bias
Is the percentage of missing values adequate? (less < 30%)
For association studies: 19. Was the outcome measure adjusted for potential confounders in the analysis?
For prediction studies: 20. Were multivariable analyses performed? If yes 21. Was it clearly described which variables were included in the (multivariable) model(s)?
Final question
22. Were there any other important flaws in the design or analyses of the study?

Appendix 2 Quality assessment

Appendix 3: level of Evidence

Findings	Level of evidence
Consistent findings in multiple (≥2) high quality studies	Strong evidence (S)
Consistent findings in one high quality study and at least one moderate quality study or consistent findings in multiple moderate quality studies.	Moderate evidence (M)
Only one study available or inconsistent findings in multiple studies (≥2)	Inconsistent evidence (I)

CHAPTER 7

Needs and preferences regarding health care delivery as perceived by patients with Systemic Sclerosis

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A.A. Schouffoer, E.J.M. Zirkzee, S.M. Henquet, M.A.A. Caljouw, G.M. Steup-Beekman, J.M. van Laar, T.P.M. Vliet Vlieland.

Abstract

Objective: To examine the needs and preferences regarding the delivery of health care services and information provision and their determinants in patients with systemic sclerosis (SSc).

Methods: A questionnaire was sent to 77 SSc-outpatients, comprising 27 items on health care needs within the domains physical, psychological, social support, employment/ daily activities or other health problems and 13 items on information needs. Moreover, the patients' preferences regarding the provision of health care services and information were listed. Additional assessments included sociodemographic characteristics, physical functioning (SSc-Health Assessment Questionnaire) and quality of life (Short Form-36; SF-36).

Results: Sixty-four patients (83%) returned the questionnaire. Twenty-six patients (41%) reported one or more unmet health care needs, with the highest proportions of patients with unmet needs seen in the physical (28%) and psychological (20%) domain. The highest percentages of patients with information needs were observed for medical subjects (20-28%). A lower mental component summary scale score and younger age were associated with the presence of at least one health care need in the psychological domain. Worse physical functioning, a diagnosis of diffuse SSc and having a partner were associated with higher information need score. A yearly, standardized multidisciplinary assessment program was most frequently mentioned as a preferred, but not yet existing health care model (59%) and the rheumatologist as a preferred source of information supply (75%).

Conclusion: Unmet health care and information needs are common among SSc-patients. To improve SSc-health care more attention should be paid to health care services for specific physical and psychological problems and medical information supply by the rheumatologist. In addition, the development of new models of care, such as a yearly, standardized multidisciplinary diagnostic program seems warranted.

Introduction

Systemic sclerosis (SSc) is a multisystem disease of unknown origin characterized by fibrosis of the skin and considerable morbidity (15). Patients may suffer from dysfunction of lungs, kidneys, heart, gastrointestinal tract and the musculoskeletal system, as well as digital ulcers, Raynaud's phenomenon and joint contractures. Two major subtypes are distinguished; diffuse SSc with skin thickening proximal to elbow and knees, and limited cutaneous SSc with involvement of the distal extremities. Given the complexity of the disease, SSc-patients require multidisciplinary treatment by specialty physicians, health professionals such as physical therapists, occupational therapists, dieticians and psychologists (3;12;18). In recent years, SSc specific educational and rehabilitation programs have been developed (2;7;24).

Until now, little is known about how the available services relate to the health care needs of patients with SSc themselves. Rubenzik (23) found health care needs in the psychological/spiritual/existential domain in a group of 25 patients with SSc. In addition, in a Dutch study in 123 patients with SSc, the need for practical information on disease background, medication usage and dealing with pain was identified (25). However, in both studies it remained unclear to what extent the patients' needs were met by current health care services delivery. Moreover, the association between needs and patient characteristics has only in part been studied (23). None of these studies evaluated the patients' preferences regarding the provision of their care, including their views on the institution of services that are not yet available.

The aim of this study was to identify unmet health care and information needs and their determinants as well as preferences for health care services delivery and information provision in patients with SSc.

Patients and methods

Study design

The study had a cross-sectional design. Ethical approval for this study was obtained from the Institutional Review Boards of the Leiden University Medical Center. All participants gave written informed consent.

Patients

Patients were recruited between May and July 2007. Inclusion criteria were: diagnosis of SSc as established by their treating rheumatologist according to ACR criteria (1), current treatment in the Leiden University Medical Center, being able to comprehend the Dutch questionnaire and age 18 years or older. A questionnaire was sent to all patients fulfilling these criteria, accompanied by an invitation letter, an information leaflet explaining the aim and the methods of the study and a consent form. A follow-up letter was sent to participants who did not return the surveys within a month.

Assessment methods

Survey on health care and information needs and preferences.

a. Health care needs

Based on the Systemic Lupus Erythematosus Needs Questionnaire (SLENQ)(21), we developed a questionnaire including health problems relevant for patients with SSc within the following domains: physical (12 items), psychological (9 items), social support (3 items), and daily living/employment (3 items). In addition to the 12 physical items, patients were invited to report 'other physical issues' in 2 text fields, in case these were not covered by the previous items. With every item, patients were asked to score the presence of a problem (no/sometimes/frequently/always; range 0-3). Per domain, the number of problems per patient was computed (score ranges physical domain 0-42, psychological domain 0-27, social domain 0-9 and daily living employment domain 0-9). In addition, a total problem score was calculated (range 0-87).

If a problem was present, patients were then asked if they had discussed it with a health care provider (yes/no) and if not, whether there was an unmet need for contact with a health care provider regarding this problem (yes/no). A total score of unmet health care needs could be computed by adding up the number of unmet needs, ranging from 0 to 29.

The internal consistency of the questionnaire and its subscales was determined by computing Cronbach's alpha for the health care problem score. In general, a Cronbach's alpha of ≥0.70 is considered acceptable. For scales with a small number of items (social support and daily living/employment) and a low Cronbach's alpha, a mean inter-item correlation was computed (optimal range recommended 0.2 to 0.4). Cronbach's alpha of the total health care problem questionnaire was 0.90, whereas for the subscales Cronbach's alpha was 0.79 for the physical domain, 0.89 for the psychological domain, 0.54 for the social support domain (inter-item correlation 0.34), and 0.78 for the daily living/employment domain.

As there is no gold standard for perceived health care needs, we determined the convergent validity of the questionnaire by examining the association between problem scores of the questionnaire and measures of physical and mental functioning. For this purpose, correlations were computed between the problem score of the physical domain on the one side and the Physical Component Summary Scale of the SF-36; PCSS) and disability (HAQ score) on the other side and between the problem score of the psychological domain and the Mental Component Summary Scale of the SF-36 (MCSS) (Pearson correlation coefficients). There were significant correlations between the physical symptoms score on the one side and the PCSS ($r=-0.603$, $p<0.01$) and the HAQ ($r- 0.598$, $p<0.01$) on the other side and between the psychological symptoms score and the MCSS ($r=-0.740$, $p<0.01$)

b. Information needs.

Again based on the SLENQ (21), 13 questions assessed the need for information on the following topics: Test results, Medical treatment of SSc, Knowing when to see a doctor, General information on medical tests, Information on SSc, Physical therapy, Exercise and sports, the SSc patients society, Occupational therapy, Dental health, Dietary information, Counseling services, Home (nursing) care. As compared to the SLENQ, the questions about physical activities and sports, physical therapy and home (nursing) care were added. With every topic, the information need was scored on a five-point Likert scale: 1= no need, 2=low need, 3=indifferent, 4=moderate need, 5= high need. The scores were later dichotomized in two categories in the same manner as was done in the SLENQ: 0 'no need, low need or indifferent' and 1 'moderate or high need', so a total information need score could be computed, ranging from 0 to 13.

c. ***Preferences for health care delivery specifically for patients with SSc.***

Patients' preferences regarding the delivery of health care in addition to regular outpatient clinic care included the following options: (i) multidisciplinary treatment if needed; (ii) a yearly multidisciplinary diagnostic program with standardized measurement of disease activity and other medical assessments; (iii) a yearly multidisciplinary diagnostic program with standardized measurement of disease activity and other medical assessments as well as an inventory of the patient's personal need for health professionals' care and information supply. Preferences were assessed on a five point scale (1= no need, 2=low need, 3=indifferent, 4=moderate need, 5= high need).

d. Preferences regarding the provision of information

Patients were asked if they were to look for information in the next year, how they would rate their preferences for the following sources of information: internet, written information (leaflets), others coping with SSc, patient support group, information meeting in the hospital, group educational program (with or without family present), rheumatologist, general practitioner or nurse specialist. Preference was evaluated by a five point scale (1=not at all preferred -5=highly preferred).

An expert panel of three rheumatologists (AAS, GSB, JMvL) and a physician/ epidemiologist (TVV) was responsible for the translation and adaptation of the SLENQ and the development of additional questions concerning preferences. Pilot-testing by two SSc patients resulted in a few minor adjustments of the final questionnaire (appendix 1).

Socio-demographic characteristics

Socio-demographic variables included age, (status of living (living with a partner yes/ no), educational level: primary education (0-8 years; low education level), secondary

education (9-16 years; medium education level) and higher vocational education/ university (post secondary; high education level) and paid employment (yes/no).

Disease characteristics and function

Disease duration and disease subset (limited or diffuse) (15), were derived from the medical record. Disease onset was defined as time since diagnosis by the rheumatologist in either the Leiden University Medical Cennter (LUMC) or if applicable in another medical centre (in years). In addition, patients were asked to fill in the SSc Health Assessment Questionnaire (SSc HAQ), a 20-item questionnaire comprising eight domains of activities of daily living, with the final score ranging from 0 (no disability) to 3 (severe disability) with scleroderma-symptom visual analogue scales (VAS 0-100 mm) in addition; Raynaud's disease, digital ulcers, intestinal complaints, pulmonary complaints, overall complaints, and pain (4).The SSc HAQ has been found to be a reliable outcome measure for disease severity in SSc (20).

Quality of life

Quality of life was measured with the Short Form-36, which includes eight domain scores: physical functioning, role limitation due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitation due to emotional problems, and mental health. The scores of the SF-36 subscales range from 0-100, with higher scores indicating better quality of life. The subscales can be converted into two summary scales: the physical and mental component summary scale, standardized to a score with a mean of 50 and a standard deviation of 10 in the general population. For that purpose, we used the scores from an age- and sex-matched, normative sample, drawn from a large, random, nationwide sample of adults (n=1742) from the general Dutch population Frequency Table and factor score coefficients (26). The psychometric properties of this questionnaire have been found to be adequate (6).

Data analysis

Data entry was performed using Microsoft Office Access 2003. Statistical analyses were executed using SPSS 16.0 software. Frequencies or means and standard deviations were calculated for each sociodemographic measure and disease characteristic, where appropriate. Comparisons of sociodemographic and disease characteristics of patients with limited and diffuse SSc were done with unpaired t-tests, Chi-Square or Fisher's exact tests, where appropriate.

Descriptive statistics were employed for the patients' needs and preferences regarding health care services and information delivery.

To determine which factors were associated with health care needs, logostic regression analysis was performed with socio-demographic and disease characteristics as independent variables and the health care need score, dichotomized into no need (0) and at least 1 need (≥1) as dependent variable. This analysis was repeated for each

domain with the domain score dichotomized into no need (0) and at least 1 need (≥1) as dependent variable. To determine which factors were associated with information needs, linear regression analysis was performed, with socio-demographic and disease characteristics as independent variables and the information need score as dependent variable.

Table 1. Sociodemographic and disease characteristics of 64 patients with Systemic Sclerosis

	Total sample, N= 64	Diffuse SSc, N=34	Limited SSc, N=30
Age, years ; mean (SD)	55.3 (13.2)	53.1 (10.7)	57.8 (15.5)
Female, N (%)	50 (78) [a]	23 (68%)	27 (90%)
Disease duration, years ; mean (SD)	8.5 (6.4) [†]	6.4 (4.7)	10.3 (7.3)
ANA/ anti-Scl70/ anti-centromere/ anti-RNP	55/ 22[a]/ 5/ 9	29/ 17/ 2/ 3	26/ 5/ 3/ 6
ESR, mm; median, mean (SD)	23.6 (16.0)	22.1 (14.7)	25.4 (17.5)
CRP, mg/dl; median, (25th–75th percentile)	4 (3-7)[a]	5 (3-9)	3 (3-7)
Creatinin, umol/l; mean (SD)	78.3 (33.7)	79.2 (26.6)	77.1 (41.0)
Interstitial lung disease, N	37[†]	24	13
Vital Capacity, % expected; mean (SD)	92.0 (19.3)[a]	85.8 (18.4)	100.2 (17.6)
Pulmonary hypertension, N	2	1	1
SSc-HAQ (0-3); median (25th–75th percentile)	0.63 (0.25-1.12)	0.63 (0.25-1.19)	0.63 (0.25-1.31)
VAS Raynaud's disease (0-100 mm)	28 (12-59)	21 (6-58)	30 (19-74)
VAS digital ulcers (0-100 mm)	4 (0-40)	0 (0-31)	11 (0-67)
VAS intestinal complaints (0-100 mm)	13 (0-44)	12 (0-43)	18 (0-46)
VAS pulmonary complaints (0-100 mm)	20 (0-54)	32 (0-57)	15 (0-48)
VAS overall complaints (0-100 mm)	29 (10-53)	29 (11-60)	26 (8-49)
VAS pain (0-100 mm)	23 (5-52)	24 (5-48)	19 (8-78)
SF-36; median, (25th–75th percentile)			
Physical Component Summary Scale	43.8 (34.6-52.6)[b]	43.8 (33.1-54.5)	43.5 (34.6-51.7)
Mental Component Summary Scale	53.3 (43.6-63.0)	57.6 (47.9-63.8)	52.7 (41.4-59.9)
Living with partner, N (%)	46 (72)	23 (68)	23 (77)
Education level , N (%)			
Low	26 (41)	11 (32)	15 (50)
Medium	24 (38)	13 (38)	11 (37)
High	11 (17) [°]	8 (23)	3 (10)
Paid employment, N (%)	22 (34)	14 (41)[d]	8 (27)
Internet access , N (%)	50 (78)[e]	29 (85)	21 (70)

SSc systemic Slerosis, N number, SD standard deviation, HAQ Health Assessment Questionnaire, VAS visual analogue scale, SF-36 Short Form-36; [a] p<0.05 diffuse compared to limited cSSc , [b] Data not available for five diffuse and four limited cSSc patients, [c] Data not available for two diffuse and one limited cSSc patients, [d] Data not available for nine diffuse SSc patients, [e] Data not available for one diffuse and five limited SSc patients

Table 2. Presence of health problems, current care and unmet health care needs in 64 patients with systemic sclerosis.

	a. Problem present, N (%)	b. Problem has not been discussed with health care provider, N (% a)	c. Patient has not discussed the problem with health care provider, but would have liked to; unmet needs, N (% b).
Physical Domain			
1. Lung problems	31 (48)	9 (29)	1 (11)
2. Digital ulcers	25 (39)	5 (20)	0
3. Gastro-intestinal complaints	39 (61)	19 (49)	6 (32)
4. Pain	49 (77)	25 (51)	7 (28)
5. Dealing with cold fingers	58 (91)	30 (52)	7 (23)
6. Impaired strength	38 (59)	21 (55)	5 (24)
7. Difficulty swallowing	26 (41)	14 (54)	2 (14)
8. Headache	24 (38)	18 (75)	4 (22)
9. Tiredness	59 (92)	43 (73)	9 (21)
10. Dry mouth	39 (61)	28 (74)	4 (14)
11. Sleeping problems	42 (66)	33 (77)	4 (12)
12. Difficulty thinking clearly	29 (45)	25 (86)	1 (4)
Other physical problems (1)	28 (43)	7 (25)	5 (71)
Other physical problems (2)	13 (20)	3 (23)	1 (33)
Number of patients ≥1 need 18 (28%)			
Psychological Domain			
1. Worried about appearance	31 (48)	25 (81)	6 (25)
2. Uncertain regarding future	43 (67)	35 (81)	8 (23)
3. Fear of physical disability	45 (70)	22 (49)	7 (32)
4. Feeling lonely	24 (36)	19 (83)	4 (19)
5. Fear of disease progression	39 (61)	28 (72)	5 (18)
6. Feeling useless	26 (41)	22 (85)	3 (14)
7. Unable to do things you used to do	39 (61)	31 (79)	4 (13)
8. Feeling out of control	26 (41)	23 (88)	1 (4)
9. Feeling down/depressed	35 (55)	28 (80)	1 (4)
Number of patients ≥1 need 13 (20%)			
Social Domain; difficulty with			
1. Maintaining friendship	13 (20)	10 (77)	3 (30)
2. Coping with changes in sexual relation	35 (55)	28 (80)	6 (21)
3. support of family/friends	*	21	2 (10)
Number of patients ≥1 need 9 (14%)			
Daily living/Employment Domain; difficulty with			
1. Maintaining job/study performance	46 (72)	32 (70)	4 (13)
2. Keeping appointments*	25 (39)	19 (76)	1 (5)
3. Work around the house	31 (48)	19 (61)	1 (5)
Number of patients ≥1 need 4 (6%)			
All Domains			
Number of patients ≥1 need 26 (41%)			
Median number of needs 3 (1-17) (n=26)			

* number of patients unknown due to lack of clarity in question

Results

Sociodemographics and disease characteristics

48/77 patients responded to the initial mailing. After a reminder another 16 returned the questionnaire, resulting in 64 responders (83%), 4 male and 9 female non-responders. Socio-demographic and disease characteristics are presented in Table 1. In the limited SSc group there were more females (p=0.031) and patients with limited SSc had a significantly longer disease duration than patients with diffuse SSc (p=0.019). There were no statistically significant differences in any other socio-demographic or disease characteristics between the two groups of patients.

Unmet health care needs

Table 2 presents the frequencies of reported health problems in the physical, psychological, social support and daily living/employment domains, contacts with physicians and/or health professional, and unmet health care needs regarding these issues. 'Tiredness' (92%) and 'Dealing with cold fingers' (91%) were problems that were most frequently mentioned. In total, twenty-six patients (41%) reported one or more unmet health care needs regarding the above mentioned problems. The mean score for the physical problem scale was 17.2 (SD 8.1), psychological problem scale 6.7 (SD 5.3), daily living/employment problem scale 2.4 (SD 2.0), and social support 2.0 (SD 1.9), total problem score 28.3 (SD 14.0).

The highest percentages of patients with an unmet need were seen within the physical domain. The highest percentages of patients indicating at least one need was observed in the physical domain (28%), followed by the psychological (20%), social (14%) and daily living/employment (6%) domains.

Associations between sociodemographic and disease characteristics and health care needs

None of the socio-demographic and disease characteristics were significantly associated with a higher overall health care need (see Table 3). Patients with least one need in the physical domain were younger (50.3 (SD 16.1) versus 57.2 (11.5), although the association was not significant (OR 0.96 (95%CI 0.92 to 1.0), p=0.69). For the psychological domain, a lower mental component summary scale score (OR 0.92 (95%CI 0.87 to 0.99), p=0.02 and younger age (OR 0.92; 95%CI 0.87 to 0.98), p=0.01 were significantly associated with a higher health care need (Results not shown).

Information needs

Table 4 shows the results of the patients' needs regarding information. In the total group, the median total information need score was 6 (range 0-13). Fifty-five patients (86%) reported an information need regarding one or more of the 13 items. The topics

Table 3. Association between the presences of at least one healthcare need (in either the physical, psychological, social, daily living domain) and socio-demographic and disease characteristics in 64 systemic sclerosis patients.

	No need	≥ 1 Need	OR (95% CI)
Age (years), mean (SD)	57.7 (12.0)	51.7 (14.6)	0.96 (0.92, 1.0)
Female gender (% total)	29 (76)	21 (81)	1.3 (0.38, 4.45)
Partner present (% total)	27 (71)	19 (68)	0.90 (0.30, 2.76)
Diffuse subtype SSc (% total)	21 (55)	13 (50)	0.81 (0.30, 2.20)
Disease duration (years), mean (SD)	8.8 (6.7)	7.4 (5.9)	0.97 (0.89, 1.05)
HAQ (range 0-3), mean (SD)	0.81 (0.71)	0.77 (0.69)	0.84 (0.44, 1.93)
Education, N (% total)			
Low	16 (62)	10 (39)	reference
Medium	14 (58)	10 (42)	0.75 (0.18, 3.12)
High	6 (55)	5 (46)	0.86 (0.20, 3.61)
SF-36, 0-100, mean (SD)			
PCSS	43.7 (13.2)	43.9 (9.2)	1.0 (0.96, 1.05)
MCSS	55.5 (10.8)	50.1 (11.3)	0.95 (0.91, 1.01)*

OR= Odds Ratio; CI= confidence interval; SSc= Systemic Sclerosis; HAQ= Health Assessment Questionnaire; SF-36= Short Form-36; PCSS= Physical Component Summary Scale; MCSS= Mental Component Summary Scale; * p=0.088

Table 4. Information needs of 64 patients with systemic sclerosis*, N (%)

	No need	Low need	Indifferent	Moderate need	High Need
Test results	1 (2)	5 (8)	5 (8)	30 (47)	18 (28)
Medical treatment of SSc	4 (6)	8 (12)	10 (16)	22 (34)	16 (25)
Knowing when to see a doctor	4 (6)	8 (13)	10 (16)	23 (36)	15 (23)
Medical tests you need	2 (3)	6 (9)	9 (14)	31 (48)	13 (20)
Information on SSc,	8 (13)	10 (16)	15 (23)	17 (27)	11 (17)
Physical therapy	6 (9)	14 (22)	10 (16)	18 (28)	10 (16)
Exercise and sports	7 (11)	15 (23)	10 (16)	17 (27)	9 (14)
SSc society	15 (23)	14 (22	10 (15)	9 (14)	7 (11)
Occupational therapist	12 (19)	11 (17)	10 (16)	20 (31)	6 (9)
Dental health	9 (14)	14 (22)	13 (20)	13 (20)	5 (8)
Dietary information	10 (16)	14 (22)	13 (20)	13 (20)	5 (8)
Counseling services	10 (16)	18 (28)	15 (23)	7 (11)	4 (6)
Home (nurse) care	12 (19)	17 (27)	15 (23)	10 (16)	4 (6)

* numbers of patients and percentages, missing numbers not listed

showing the highest proportions of patients with a moderate or high information need included: test results (75%), medical tests you need (68%), medical treatment of SSc (59%) and knowing when to see a doctor (59%). A higher information need was significantly associated with diffuse SSc (adjusted for disease duration; Beta 2.4, 95%CI 0.1 to 4.6, p=0.039), a lower physical component summery scale SF-36 (Beta 0.09, 95% CI 0.01 to 0.05, p=0.048) and having a partner (Beta 2.6, 95% CI 0.5 to 5.1, p=0.046).

Preferences regarding specific health care services additional to regular outpatient clinic care.

Table 5 shows the proportion of patients interested in specific forms of the delivery of multidisciplinary services specifically for patients with SSc. Overall, 45/64 (70%) of the patients had a moderate or high need for at least one of the comprehensive services specifically for SSc
patients.

Preferences regarding the provision of information

The rheumatologist was indicated as the preferred source of information in the nearby future by 75% of the patients (Table 6). Leaflets/books (63%), the Internet (61%) and group educational program in the hospital (58%) were more frequently indicated as a desired method of information delivery than information meetings organized by the Dutch Society of SSc patients, individual information provision by medical specialists other than the rheumatologist or by clinical nurse specialists (<50%).

Table 5. Preferences for health care delivery in addition to regular outpatient clinic care of 64 patients with systemic sclerosis*

	No need	Low need	Indifferent	Moderate need	High Need
Multidisciplinary treatment planned if needed, N (%)	12 (19)	2 (3)	13 (20)	19 (30)	9 (14)
Yearly program with multidisciplinary standardized medical assessment, N (%)	5 (8)	5 (8)	8 (13)	15 (23)	23 (36)
Yearly program also including an inventory of the patient's needs regarding health professionals' care, N (%)	8 (13)	4 (6)	13 (20)	15 (23)	16 (25)

* numbers of patients and percentages, missing numbers not listed

Table 6: Preferences for the provision of information in 64 patients with systemic sclerosis, N(%)*

	No need	Low need	Indifferent	Moderate need	High Need
Rheumatologist	1 (2)	3 (5)	4 (6)	22 (34)	26 (41)
Internet	7 (11)	2 (3)	2 (3)	20 (31)	19 (30)
Brief lets/books	6 (9)	1 (2)	7 (11)	28 (44)	12 (19)
Other specialty physician or general practitioner	6 (9)	10 (16)	12 (19)	14 (22)	9 (14)

* numbers of patients and percentages, missing numbers not listed

Discussion

In this study on the needs of patients with SSc regarding the provision of health services and information, it was found that a number of patients indicated an unmet need for help regarding physical and/or mental problems. Information needs were most frequently mentioned with respect to medical issues. A substantial proportion of patients showed interest in various multidisciplinary services, and the rheumatologist was most often mentioned as the preferred provider of information.

Considering the impact of SSc on physical and psychosocial functioning and the usage of a high volume of physician services by SSc-patients (3;10) the lack of studies on patients' needs, satisfaction and preferences in health care is remarkable. In other rheumatic conditions, a high information need as well as a high percentage of unmet health care needs has been demonstrated (11;14;16).

In our study patients the highest proportion of patients with at least one unmet need was seen in the physical domain. Our findings are difficult to compare directly with the published studies on unmet needs in SSc. Rubenzik (23) evaluated the needs of 25 SSc patients, nine diffuse, nine limited and seven unsure subtype, but with the methodology employed in that study, questions based on a four-point scale (ranging from no need to high need) it remained unclear to what extent their indicated need for contact with a health professional was already satisfied. In patients with systemic lupus erythematosus (21), the physical domain had the highest proportion of participants with al least one unmet need. Rubenzik on the other hand, found high health care needs in nine out of ten items of the psychological/spiritual/existential domain and four out of 12 items in the physical domain, suggesting more needs in the psychological domain.

As compared to the needs of SLE patients (21) (where the number of patients with a need that was already satisfied were taken into account), our study demonstrate a relatively low percentage of patients with unmet needs. This may be because of the

mild functional disability as demonstrated bij SF-36 and SSc HAQ outcomes in both the diffuse and limited cSSc group.

Concerning the association between disease characteristics and health care needs, worse mental functioning was significantly associated with the presence of at least one unmet need in the psychological domain. A previous study by Rubenzik did not examine the relationship of disease characteristics and health care needs, except for subtype. In 1193 patients with rheumatoid arthritis and ankylosing spondylitis (14) unmet health care needs were likewise associated with worse health status. The lack of association between physical functioning and health care needs in our study may be were explained by the relatively mild average level of
functional disability. This may partly be due to the fact that 19 patients with diffuse systemic sclerosis had been effectively treated.

With respect to sociodemographic characteristics, in our study a younger age was significantly associated with needs in the psychological domain. Rubenzik (23) found higher need in the social domain in patients with a rural background, and a higher need in measures from the physical, psychological, daily living and social domain in patients without a partner. In patients with rheumatoid arthritis and ankylosing spondylitis (14) no association of sex or age with health care needs was seen, whereas education was not evaluated.

Our study identified a considerable proportion of patients with a need for information, in particular on medical issues, including test results, medical treatment and knowing when to see a doctor. These findings are in line with a Dutch study (25), where the need for information on various subjects was evaluated by a 4-point Likert scale. Information on SSc (mean 2.29) had the highest score, followed by medication usage (1.77) and dealing with pain (1.77). In contrast, Rubenzik (23) concluded that there was not much need for medical information, possibly because of the presumed increased publicly accessible information. Due to differences in study design, a direct comparison of the magnitude of the need for medical information between these studies is difficult. In recent years publications on unmet information needs in other rheumatic diseases have demonstrated that patients have high desire for information (14;19;22). Leung found the highest unmet information need in psoriatic arthritis was advice on exercise (68%) (16). Studies evaluating knowledge and information need of patients with rheumatoid arthritis (RA) mainly focused on the disease and on specialist medical care (9;5;17). In general, these studies report a lack in of knowledge about the disease, medical care and medication. This is partly in line with our results.

We found that more information needs were associated with a subtype SSc as well as worse physical functioning and having a partner. The latter is surprising; discussing SSc related problems with a partner may generate more information needs. Rubenzik (23) found more unmet needs in the domains health services, health information and social support in patients with less education. In patients with RA it was demonstrated the

female gender (14) and lower age (8) were predictive for the presence of information needs. A significant difference in need for information between men and women, or lower and higher education was not observed in our results.

The preferences of SSc patients regarding the provision of SSc specific health care programs and information have never been evaluated previously. Important findings are the preference of patients for their rheumatologist as source of information supply over any other type of information gathering, and the patients' interest in a yearly daycare program with standardized assessment of the disease course in addition to regular outpatient clinic care. These findings are in line with results among patients with psoriatic arthritis, showing that a large proportion of patients are motivated to participate in various additional care programs (16).

Our study has a number of limitations. First, the study group is relatively small, although the number of participants is greater than the 25 patients studied in a previously published paper on unmet needs in systemic sclerosis (23). Also, the cohort has relatively long disease duration, this is especially the case for the patients with diffuse systemic sclerosis (average 6.4 years (SD 4.7). Therefore, the group of patients could probably be considered a survival cohort, which could explain the relatively mild level of functional disability as compared to other cohorts of patients with SSc (10;13). This selection bias could hamper the generalization of our data to patients with shorter disease duration and/or more active disease. As correlations between disease activity and stage and unmet needs may be identified by a larger study group cohort, further research is warranted.

Comparison with other patients groups may further be hampered by differences in healthcare systems and socio-economic background of patients.

Second, the questionnaire we used was based on the SLENQ, but was not yet validated in Dutch. Unfortunately, data collection was established prior to publication of the study by Rubenzik, who employed the SUNI, which was also based on the SLENQ. The items included in our questionnaire and the SUNI are largely comparable, but not identical. Finally, selection bias can not be fully excluded since the response rate was 83%. On the other hand, a response rate of 83 % is relatively high, and might probably express patients' willingness to be engaged in the optimization of health care services.

In daily practice our results imply that SSc patients may face several physical or psychological problems that are, according to a considerable number of patients, not sufficiently addressed by rheumatologists. These include physical symptoms as pain and or Raynaud's phenomenon. The concurring need for guidance with respect to psychological issues, e.g. the uncertainty and fears patients that have to deal with, substantiates the need for a multidisciplinary approach. In our study it was indeed demonstrated that a substantial proportion of patients showed interest in various multidisciplinary services. Another important finding in this study is the high information need in SSc-patients, and the preference of the rheumatologist as information supplier.

This suggests that health care in SSc should also focus on patient education. In outpatient clinic care a rheumatologist can pay more attention to information supply. At the same time, patient education programs, involving a rheumatologist, may further improve the quality of SSc patient care.

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Reference List

1. (1980) Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 23:581-590
2. Antonioli CM, Bua G, Frige A, Prandini K, Radici S, Scarsi M, Danieli E, Malvicini A, Airo P (2009) An individualized rehabilitation program in patients with systemic sclerosis may improve quality of life and hand mobility. Clin Rheumatol 28:159-165
3. Bernatsky S, Panopolis P, Hudson M, Pope J, Leclercq S, Robinson D, Jones N, Markland J, bu-Hakima M, Mathieu JP, Docherty P, Khalidi N, Sutton E, Baron M (2009) Demographic and clinical factors associated with physician service use in systemic sclerosis. J Rheumatol 36:96-98
4. Clements PJ, Wong WK, Hurwitz EL, Furst DE, Mayes M, White B, Wigley F, Weisman M, Barr W, Moreland L, Medsger TA, Jr., Steen V, Martin RW, Collier D, Weinstein A, Lally E, Varga J, Weiner SR, Andrews B, Abeles M, Seibold JR (2001) The Disability Index of the Health Assessment Questionnaire is a predictor and correlate of outcome in the high-dose versus low-dose penicillamine in systemic sclerosis trial. Arthritis Rheum 44:653-661
5. Edworthy SM, Devins GM, Watson MM (1995) The arthritis knowledge questionnaire. A test for measuring patient knowledge of arthritis and its self-management. Arthritis Rheum 38:590-600
6. Essink-Bot ML, Krabbe PF, Bonsel GJ, Aaronson NK (1997) An empirical comparison of four generic health status measures. The Nottingham Health Profile, the Medical Outcomes Study 36-item Short-Form Health Survey, the COOP/WONCA charts, and the EuroQol instrument. Med Care 35:522-537
7. Genth E, Baltscheit C (2003) [Patient education "systemic sclerosis"]. Z Rheumatol 62:II24-II25
8. Gordon MM, Capell HA, Madhok R (2002) The use of the Internet as a resource for health information among patients attending a rheumatology clinic. Rheumatology (Oxford) 41:1402-1405
9. Hennell SL, Brownsell C, Dawson JK (2004) Development, validation and use of a patient knowledge questionnaire (PKQ) for patients with early rheumatoid arthritis. Rheumatology (Oxford) 43:467-471
10. Hudson M, Thombs BD, Steele R, Panopalis P, Newton E, Baron M (2009) Quality of life in patients with systemic sclerosis compared to the general population and patients with other chronic conditions. J Rheumatol 36:768-772
11. Jacobi CE, Rupp I, Boshuizen HC, Triemstra M, Dinant HJ, van den Bos GA (2004) Unmet demands for health care among patients with rheumatoid arthritis: indications for underuse? Arthritis Rheum 51:440-446
12. Johnson SR, Carette S, Dunne JV (2006) Scleroderma: health services utilization from patients' perspective. J Rheumatol 33:1123-1127
13. Khanna D, Ahmed M, Furst DE, Ginsburg SS, Park GS, Hornung R, Tsevat J (2007) Health values of patients with systemic sclerosis. Arthritis Rheum 57:86-93
14. Kjeken I, Dagfinrud H, Mowinckel P, Uhlig T, Kvien TK, Finset A (2006) Rheumatology care: Involvement in medical decisions, received information, satisfaction with care, and unmet health care needs in patients with rheumatoid arthritis and ankylosing spondylitis. Arthritis Rheum 55:394-401
15. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Jr., Rowell N, Wollheim F (1988) Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 15:202-205

16. Leung YY, Tam LS, Lee KW, Leung MH, Kun EW, Li EK (2009) Involvement, satisfaction and unmet health care needs in patients with psoriatic arthritis. Rheumatology (Oxford) 48:53-56
17. Lineker SC, Badley EM, Hughes EA, Bell MJ (1997) Development of an instrument to measure knowledge in individuals with rheumatoid arthritis: the ACREU rheumatoid arthritis knowledge questionnaire. J Rheumatol 24:647-653
18. Mawdsley AH (2006) Patient perception of UK scleroderma services--results of an anonymous questionnaire. Rheumatology (Oxford) 45:1573
19. Meesters JJ, Vliet Vlieland TP, Hill J, Ndosi ME (2009) Measuring educational needs among patients with rheumatoid arthritis using the Dutch version of the Educational Needs Assessment Tool (DENAT). Clin Rheumatol 28:1073-1077
20. Merkel PA, Herlyn K, Martin RW, Anderson JJ, Mayes MD, Bell P, Korn JH, Simms RW, Csuka ME, Medsger TA, Jr., Rothfield NF, Ellman MH, Collier DH, Weinstein A, Furst DE, Jimenez SA, White B, Seibold JR, Wigley FM (2002) Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. Arthritis Rheum 46:2410-2420
21. Moses N, Wiggers J, Nicholas C, Cockburn J (2005) Prevalence and correlates of perceived unmet needs of people with systemic lupus erythematosus. Patient Educ Couns 57:30-38
22. Neame R, Hammond A, Deighton C (2005) Need for information and for involvement in decision making among patients with rheumatoid arthritis: a questionnaire survey. Arthritis Rheum 53:249-255
23. Rubenzik TT, Derk CT (2009) Unmet patient needs in systemic sclerosis. J Clin Rheumatol 15:106-110
24. Samuelson UK, Ahlmen EM (2000) Development and evaluation of a patient education program for persons with systemic sclerosis (scleroderma). Arthritis Care Res 13:141-148
25. Teunissen, H. A., van Lankveld W.G.J.M., Vonk M.C., and van den Hoogen F.H.J. systemische sclerose: de gevolgen voor het psychisch en lichamelijk functioneren, en de behoefte aan begeleiding. nederlands tijdschrift voor reumatologie 2005(4), 33-39. 2005. Ref Type: Magazine Article
26. Ware JE KMKS (1994) SF-36 Health Survey Manual and Interpretation Guide.

VRAGENLIJST ZORGBEHOEFTEN

1. Hieronder staat een lijst met mogelijke lichamelijke problemen of ongemakken die u gehad zou kunnen hebben als gevolg van Sclerodermie. Wilt u voor elk genoemd probleem / ongemak afzonderlijk nagaan of u die in **de afgelopen 12 maanden** heeft gehad en aangeven hoe vaak en hoe in welke mate u daar last van heeft gehad. Kunt u ook aangeven of u hierover contact heeft gehad of behoefte heeft gehad aan contact met een professionele zorgverlener *(bijv.: huisarts, medisch specialist, verpleegkundige, etc*.). Indien u van het genoemde probleem/ongemak nooit last heeft gehad de afgelopen twaalf maanden dan kunt u door naar de volgende vraag. Wilt u alstublieft geen enkele vraag overslaan. *(Kruis aan welk antwoord van toepassing is.)*

1. Heeft u de afgelopen 12 maanden last gehad van **vermoeidheid**?

nooit ❑ | Dagelijks ❑ | wekelijks ❑ | maandelijks ❑

Indien u last heeft gehad van vermoeidheid, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van vermoeidheid, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

2. Heeft u de afgelopen 12 maanden last gehad van **pijn?**

nooit ❑ | dagelijks ❑ | Wekelijks ❑ | maandelijks ❑

Indien u last heeft gehad van pijn, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van pijn, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

3. Heeft u de afgelopen 12 maanden last gehad van **slecht slapen**?

nooit ❑ | dagelijks ❑ | wekelijks ❑ | maandelijks ❑

Indien u last heeft gehad van slecht slapen, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daar last van heeft gehad.

helemaal niet _____ heel ergIndien u last heeft gehad van slecht slapen, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

4. Heeft u de afgelopen 12 maanden last gehad van **een droge mond**?

nooit ❑ | dagelijks ❑ | Wekelijks ❑ | maandelijks ❑

Indien u last heeft gehad van een droge mond, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van een droge mond, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

5. Heeft u de afgelopen 12 maanden last gehad van **longproblemen**?

nooit ❑ | dagelijks ❑ | Wekelijks ❑ | maandelijks ❑

Indien u last heeft gehad van longproblemen, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van longproblemen, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

6. Heeft u de afgelopen 12 maanden last gehad van **krachtverlies**?

nooit ❑ | dagelijks ❑ | Wekelijks ❑ | maandelijks ❑

Indien u last heeft gehad van krachtverlies, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van krachtverlies, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

7. Heeft u de afgelopen 12 maanden last gehad van **concentratiestoornis**?

nooit	dagelijks	wekelijks	Maandelijks
❑	❑	❑	❑

Indien u last heeft gehad van **concentratiestoornis**, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van **concentratiestoornis**, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

8. Heeft u de afgelopen 12 maanden last gehad van **koude gevoelloze handen**?

nooit	dagelijks	wekelijks	Maandelijks
❑	❑	❑	❑

Indien u last heeft gehad van koude gevoelloze handen, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van koude gevoelloze handen, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

9. Heeft u de afgelopen 12 maanden last gehad van **wondjes aan de vingers**?

nooit	dagelijks	wekelijks	Maandelijks
❑	❑	❑	❑

Indien u last heeft gehad van wondjes aan de vingers, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van wondjes aan de vingers, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

10. Heeft u de afgelopen 12 maanden last gehad van **maag en darm problemen**?

nooit	dagelijks	wekelijks	Maandelijks
❑	❑	❑	❑

Indien u last heeft gehad van maag en darm problemen, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van maag en darm problemen, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

11. Heeft u de afgelopen 12 maanden last gehad van **slikproblemen/passageklachten**?

nooit	dagelijks	wekelijks	Maandelijks
❑	❑	❑	❑

Indien u last heeft gehad van slikproblemen/passageklachten, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van slikproblemen/passageklachten, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

12. Heeft u de afgelopen 12 maanden last gehad van **hoofdpijn**?

nooit	dagelijks	wekelijks	Maandelijks
❑	❑	❑	❑

Indien u last heeft gehad van hoofdpijn, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van hoofdpijn, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

13. Zijn er andere lichamelijk problemen waar u de afgelopen 12 maanden last van hebt gehad?
Bij deze vraag kunt u indien van toepassing 1of 2 problemen vermelden. Per probleem kunt u aangeven hoeveel last u er van heeft gehad en of u contact heeft gehad met een professionele zorgverlener.

❑ nee
❑ ja, namelijk van _____

Kunt u aangeven in welke mate u van dit lichamelijke probleem last heeft gehad?

nooit	dagelijks	wekelijks	Maandelijks
❑	❑	❑	❑

Indien u last heeft gehad van dit probleem, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daarvan last heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van dit probleem, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

❑ ja, namelijk van _____

Kunt u aangeven in welke mate u van dit lichamelijke probleem last heeft gehad?

nooit	dagelijks	Wekelijks	Maandelijks
❑	❑	❑	❑

Indien u last heeft gehad van dit probleem, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen 12 maanden** daarvan last heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van dit probleem, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

2. Hieronder volgt een lijst met mogelijke emotionele en cognitieve problemen die u gehad zou kunnen hebben door de SLE/Sclerodermie. Wilt u voor elk genoemd probleem afzonderlijk nagaan of u dat in **de afgelopen maand** heeft gehad en aangeven hoe vaak en in welke mate u daar last van heeft gehad. Kunt u ook aangeven of u hierover contact heeft gehad of behoefte heeft gehad aan contact met een professionele zorgverlener *(bijv.: huisarts, medisch specialist, verpleegkundige, etc*.)? Indien u van het genoemde probleem nooit last heeft gehad de afgelopen maand dan kunt u door naar de volgende vraag. Wilt u alstublieft geen enkele vraag overslaan. *(Kruis aan welk antwoord van toepassing is.)*

1. Heeft u zich de afgelopen maand **neerslachtig** gevoeld?

nooit	soms	regelmatig	altijd
❑	❑	❑	❑

Indien u last heeft gehad van **neerslachtigheid**, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate (hoe erg) u in de **afgelopen maand** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien u last heeft gehad van neerslachtigheid, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee ❑ nee

2. Is het de afgelopen maand voorgekomen dat u niet in staat was de **gebruikelijke dingen** te doen?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien het is voorgekomen dat u niet in staat was de **gebruikelijke dingen** te doen, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen maand** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien het is voorgekomen dat u niet in staat was de gebruikelijke dingen te doen heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

3. Is het de afgelopen maand voorgekomen dat u zich **eenzaam** gevoeld heeft?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien het is voorgekomen dat u zich **eenzaam** heeft gevoeld, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen maand** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien het is voorgekomen dat u zich eenzaam hebt gevoeld heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

4. Is het de afgelopen maand voorgekomen dat u **bang** was dat de ziekte zou verergeren?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien het is voorgekomen dat u **bang** was dat de ziekte zou verergeren, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen maand** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien het is voorgekomen dat u bang was dat de ziekte zou verergeren heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

5. Is het de afgelopen maand voorgekomen dat u **onzeker** was **over de toekomst**?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien het is voorgekomen dat u **onzeker** was **over de toekomst**, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen maand** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien het is voorgekomen dat u onzeker was over de toekomst heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

6. Is het de afgelopen maand voorgekomen dat u zich zorgen maakte over **lichamelijke beperkingen**?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien het is voorgekomen dat u zich zorgen maakte over **lichamelijke beperkingen**, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen maand** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien het is voorgekomen dat u zich zorgen maakte over lichamelijke beperkingen heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

7. Is het de afgelopen maand voorgekomen dat u zich zorgen maakte over **veranderingen in uw uiterlijk**?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien het is voorgekomen dat u zich zorgen maakte over **veranderingen in uw uiterlijk**, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen maand** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien het is voorgekomen dat u zich zorgen maakte over veranderingen in uw uiterlijk heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

8. Is het de afgelopen maand voorgekomen dat u zich **nutteloos** voelde?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien het is voorgekomen dat u zich **nutteloos** voelde, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen maand** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien het is voorgekomen dat u zich nutteloos voelde heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

9. Heeft u de afgelopen maand het gevoel gehad niet **alles onder controle** te hebben?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien het is voorgekomen dat u het gevoel had **niet** altijd alles onder controle te hebben, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen maand** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien het is voorgekomen dat u het gevoel had **niet** altijd alles onder controle te hebben heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

3. Hieronder volgen een aantal problemen/beperkingen of veranderingen op sociaal en maatschappelijk gebied die door uw ziekte veroorzaakt kunnen zijn. Wilt u voor elk genoemd probleem/beperking of verandering afzonderlijk nagaan of het in **de afgelopen 12 maanden** voor u van toepassing was en aangeven hoe vaak en in welke mate u daar last van heeft gehad. Kunt u ook aangeven of u hierover persoonlijk contact heeft gehad of behoefte heeft gehad aan contact met een professionele zorgverlener *(bijv.: huisarts, medisch specialist, verpleegkundige, etc*.). Indien u van het genoemde probleem/ongemak nooit last heeft gehad de afgelopen twaalf maanden dan kunt u door naar de volgende vraag. Wilt u alstublieft geen enkele vraag overslaan. *(Kruis aan welk antwoord van toepassing is.)*

1. Heeft u de laatste **12 maanden** problemen gehad bij het uitoefenen van uw werk/studie of dagelijkse bezigheden?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien u problemen heeft gehad bij het uitoefenen van uw werk/studie of dagelijkse bezigheden, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u de afgelopen **12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien u problemen hebt gehad bij het uitoefenen van uw werk/studie of dagelijkse bezigheden, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

2. Is het de afgelopen **12 maanden** voorgekomen dat u niet in staat was gemaakte afspraken of verplichtingen na te komen vanwege uw ziekte?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien het is voorgekomen dat u niet in staat was gemaakte afspraken of verplichtingen na te komen, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen maand** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien het is voorgekomen dat u niet in staat was gemaakte afspraken of verplichtingen na te komen heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

3. Zijn er de afgelopen **12 maanden** veranderingen geweest in de door u uit voeren taken thuis?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien het is voorgekomen dat er veranderingen in de door u uit te voeren taken zijn geweest, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de afgelopen **12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien het is voorgekomen dat er veranderingen in de door u uit te voeren taken op het werk/studie of thuis zijn geweest, heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

4. Is het de afgelopen **12 maanden** voorgekomen dat u door uw ziekte problemen kreeg in uw relatie met anderen *(bijvoorbeeld partner, kinderen, familie, vrienden of kennissen)*?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien het is voorgekomen dat u door uw ziekte problemen kreeg in uw relatie met anderen, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u de afgelopen **12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien het is voorgekomen dat u door uw ziekte problemen kreeg in uw relatie met anderen heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

5. Heeft u de laatste **12 maanden** problemen gehad op seksueel gebied?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien het is voorgekomen dat u door uw ziekte problemen kreeg op seksueel gebied, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u de afgelopen **12 maanden** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien het is voorgekomen dat u door uw ziekte problemen kreeg op seksueel gebied heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

6. Heeft u de laatste **12 maanden** voldoende steun en begrip gekregen van de mensen uit uw omgeving?

nooit	soms	Regelmatig	altijd
❑	❑	❑	❑

Indien het is voorgekomen dat u geen of te weinig steun en begrip de laatste 12 maanden van mensen uit uw omgeving hebt gekregen, kunt u dan op de onderstaande lijn met een kruisje (X) aangeven in welke mate u in de **afgelopen maand** daar last van heeft gehad.

helemaal niet _____ heel erg

Indien het is voorgekomen dat u geen of te weinig steun en begrip de laatste 12 maanden van mensen uit uw omgeving hebt gekregen heeft u dan hierover persoonlijk contact gehad met een professionele zorgverlener?

❑ ja
❑ nee ⟶ heeft u hieraan wel behoefte gehad?
❑ ja
❑ nee

VRAGENLIJST ZORGAANBOD

1. Hieronder volgen enkele vragen over **uw behoefte aan informatie** over Sclerodermie.
Wilt u voor **alle** uitspraken aangeven in hoeverre u het er mee eens bent.

Ik heb behoefte aan **meer informatie over:**	helemaal oneens	oneens	niet eens / niet oneens	eens	helemaal eens
1. … de ziekte Sclerodermie	❑	❑	❑	❑	❑
2. ... de medische behandeling van Sclerodermie	❑	❑	❑	❑	❑
3. ... bij welke veranderingen in mijn gezondheidstoestand ik een arts moet raadplegen	❑	❑	❑	❑	❑
4. ... het belang van bloedonderzoek en andere onderzoeken	❑	❑	❑	❑	❑
5. … de betekenis van de uitslagen van bloedonderzoek en andere onderzoeken	❑	❑	❑	❑	❑
6. ... de thuiszorg (huishoudelijke ondersteuning, wijkverpleging, e.d.)	❑	❑	❑	❑	❑
7. ... hulpmiddelen, voorzieningen, vergoedingen en aanpassingen in huis	❑	❑	❑	❑	❑
8. ... lichamelijke activiteit en sport	❑	❑	❑	❑	❑
9. ... oefentherapie en fysiotherapie	❑	❑	❑	❑	❑
10. ...ergotherapie	❑	❑	❑	❑	❑
11. ...de mondhygiënist	❑	❑	❑	❑	❑
12. ...de diëtist	❑	❑	❑	❑	❑
13. ...de reumaconsulent	❑	❑	❑	❑	❑
14. ...het maatschappelijk werk	❑	❑	❑	❑	❑
15. …patiëntenverenigingen en lotgenotencontact	❑	❑	❑	❑	❑

2. De volgende vragen gaan over **de manier waarop u het liefst informatie wilt ontvangen.** Wilt u voor **alle** uitspraken aangeven in hoeverre u het er mee eens bent.

Als ik meer informatie over Sclerodermie wil krijgen dan zou ik in de komende twaalf maanden gebruik willen maken van:	helemaal oneens	oneens	niet eens / niet oneens	eens	helemaal eens
a. Internet (een website)	❑	❑	❑	❑	❑
b. Folders of boeken	❑	❑	❑	❑	❑
c. Lotgenotencontact (persoonlijk contact met andere patiënten)	❑	❑	❑	❑	❑
d. Informatiebijeenkomsten georganiseerd door de patiëntenvereniging	❑	❑	❑	❑	❑
e. Informatiebijeenkomsten georganiseerd door het ziekenhuis	❑	❑	❑	❑	❑
f. Een groepsvoorlichtingsprogramma georganiseerd door het ziekenhuis	❑	❑	❑	❑	❑
g. Via mijn behandelend reumatoloog	❑	❑	❑	❑	❑
h. Via een andere behandelend medisch specialist of de huisarts	❑	❑	❑	❑	❑
i. Via een gespecialiseerd verpleegkundige	❑	❑	❑	❑	❑

3. De afdeling Reumatologie van het LUMC wil met de resultaten van dit onderzoek een **zorgprogramma** gaan ontwikkelen voor mensen met Sclerodermie. Graag willen we u vragen de onderstaande vragen te beantwoorden, zodat we weten op welke wijze we het zorgprogramma kunnen invullen.

A. Als de volgende vormen van zorg beschikbaar zouden zijn, dan zou ik in de komende twaalf maanden gebruik willen maken van:

	helemaal oneens	oneens	niet eens / niet oneens	eens	helemaal eens
Een multidisciplinaire dagbehandeling in het LUMC.	❑	❑	❑	❑	❑
Een jaarlijkse, uitgebreide controle van mijn medische situatie (naast de gebruikelijke bezoeken aan de reumatoloog en/of andere medisch specialisten) in het LUMC.	❑	❑	❑	❑	❑
Een jaarlijkse, uitgebreide controle van mijn persoonlijke situatie en mijn behoefte aan zorg of begeleiding (naast de gebruikelijke contacten met mijn zorgverleners) in het LUMC	❑	❑	❑	❑	❑

CHAPTER 8

A randomized comparison of a multidisciplinary team care program with usual care in patients with Systemic Sclerosis

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A.A.Schouffoer, M.K. Ninaber, L.J.J. Beaart-van de Voorde, F.J.van der Giesen, physiotherapist[1,], Z. de Jong, J.Stolk, A.E. Voskuyl, R.W.C Scherptong, J.M. van Laar, A.J.M. Schuerwegh, T.W.J. Huizinga, T.P.M. Vliet Vlieland.

Abstract

Objective: To compare the effectiveness of a multidisciplinary team care program with usual outpatient care in patients with systemic sclerosis (SSc).

Methods: We performed a randomized controlled trial comparing a 12-week multidisciplinary team care program (1 day per week; individual treatments, group-exercises and group-education) with outpatient clinic care. Outcome measures included the HAMIS (Hand Mobility in Scleroderma), grip strength, maximal mouth opening (MMO), 6-minute walk distance (6MWD), maximum aerobic capacity (VO2max), Checklist Individual Strength (CIS-20), SSc Health Assessment Questionnaire (HAQ) and Short-form 36 (SF-36), assessed at 0, 12 and 24 weeks. Statistical comparisons of change scored included analysis of covariance.

Results: Twenty-eight patients were assigned to the intervention group (mean age 53.9 years, 15/28 diffuse SSc) and 25 to the control group (mean age 51.7 years, 15/25 diffuse SSc). Twenty-five (89%) patients in the intervention group completed the treatment program. At 12 weeks there was a significantly greater improvement in grip strength (2.2 versus -1.8 kg; p=0.001), MMO (1.4 versus -0.9 mm; p=0.011), 6MWD (42.8 versus 3.9 meter; p=0.021) and HAQ (-0.18 versus 0.13; p=0.025) in the intervention group, whereas the differences for the other outcome measures did not reach significance. At 24 weeks the effect on the grip strength persisted.

Conclusion: In patients with SSc a 12 week multidisciplinary day patient treatment program was more effective than regular outpatient care with respect to 6MWD, grip-strength, MMO and HAQ but not for $VO2_{max}$, HAMIS, CIS-20, SF 36 and visual analog scale for pain. This study provides a first step in quantifying the effect of a multidisciplinary team care program and warrants the conduct of further intervention studies.

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of multiple organs (1). Two main subtypes are distinguished: limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) (2). Despite improvements in medical treatment, SSc is associated with significant morbidity and mortality (3-6).

To help patients cope with the consequences of the disease, rehabilitative strategies are often provided. Rehabilitation in SSc may include psychoeducational interventions; exercise therapy; the application of physical modalities; assistive devices and ortheses; joint protection; and energy conservation; dietary interventions and comprehensive multidisciplinary team care interventions.

Whereas in other rheumatic conditions, especially rheumatoid arthritis (RA), the effectiveness of multidisciplinary team care has been consistently demonstrated (7), in SSc the evidence on comprehensive rehabilitation is scarce (8). A few studies demonstrated a significant improvement of measures of global health and hand function (9;10), as well as mouth function (10;11) in patients participating in a rehabilitation program. However, no direct statistical comparisons of the changes in outcome between the intervention group and control group were made. Studies on rehabilitation with single interventions as patient education (12;13), aerobic exercise (14), finger (15) or mouth (16) and hand massage and manipulation (17) showed promising results, although most of them (12-16) had a non-controlled design.

Considering the paucity of data on comprehensive rehabilitative treatment strategies in SSc, this proof-of-concept study was designed to provide preliminary evidence of efficacy of a multidisciplinary treatment team care program on multiple outcome measures reflecting the health status of patients with SSc as compared to usual outpatient care.

Patients and methods

Study design

This randomised controlled clinical trial was conducted from September 2006 until September 2008. Ethical approval was obtained from the Institutional Review Board of the Leiden University Medical Center. The patients' written informed consent was obtained at enrolment. Randomisation was performed by an independent administrative assistant by means of a four-block randomisation list, made up with a random digit generator. Patients were stratified according to the type of SSc (1). Patients allocated to the control group were offered to participate in the multidisciplinary team care program after completion of the final followup assessment.

Patients

The medical records of patients with SSc listed in the SSc-registry of our hospital and referrals from other hospitals within the enrollment period were screened for global eligibility by the principle investigator (AAS). Inclusion-criteria were: SSc according to Leroy's criteria (1), age 18-75 year, being able to cycle on a bicycle ergometer, stable anti-inflammatory medication over the past 2 months, and fluency in Dutch. Exclusion-criteria were: engagement in another exercise therapy program or concomitant diseases interfering with the performance of daily activities.

Patients fulfilling the inclusion-criteria were informed about the study and invited for a further screening to judge their exercise tolerance. The screening consisted of history taking, physical examination and the following additional investigations: blood pressure (at rest), chest radiograph, 24 hours monitoring electrocardiography, Doppler ultrasonography of the heart, exercise test by means of a bicycle ergo meter and pulmonary function testing. All test results were evaluated by a consulting cardiologist (RWCS) and pulmonologist (MKN) and, if necessary, additional examinations were scheduled.

The multidisciplinary team care program (intervention)

The multidisciplinary team care program was delivered at the day patient clinic of the department of rheumatology of a university medical center during 12 consecutive weeks, one day per week. The multidisciplinary team comprised a rheumatologist, an occupational therapist, a physical therapist, a social worker and a clinical nurse specialist. For every patient, individual treatment goals were set and discussed during 3 weekly multidisciplinary team conferences. The program consisted of standardized group sessions (general exercises, hand/mouth exercises and educational sessions) and, depending on the patients' individual needs, of individual treatments by the rheumatologist and rheumatology health professionals. In addition, patients were required to participate in individual supervised exercises provided by a physical therapist near their own home in a private practice once a week and to perform a home-based exercise program on at least 6 days per week. The program was delivered to groups with a minimum of 6 and a maximum of 10 patients (Appendix A). After completion of the multidisciplinary team care program, patients were advised to continue the exercises supervised by the local physical therapist. All other interventions or referrals after the intervention period of 12 weeks were left to the treating rheumatologist.

Safety and adherence monitoring of the multidisciplinary team care program

Safety was monitored by recording all terminations or adaptations of exercise sessions or other components of the treatment program due to pain, exertion or other reasons; adaptations were made based on a questionnaire evaluating the occurrence of pain during or after training, and the time to recovery after each group session. In addition,

any alteration in medication, in particular analgesics were recorded.

The adherence to the supervised group exercises (general and hand/mouth exercises) in the clinic and the supervised exercises at the private practices was monitored by attendance lists and records of individual progress. For the home based individual exercises (hand/mouth) a diary was filled in, with weekly evaluation by the physiotherapist in the hospital. Compliance with the group educational sessions was monitored by an attendance list kept by the clinical nurse specialist in the hospital.

Control condition

Patients in the control group received usual outpatient care as initiated by their attending rheumatologist. Attending rheumatologists had a free choice with respect to any diagnostic or therapeutic interventions including referral to a physical therapist, except for referrals to group exercises, group educational programs or multidisciplinary team care programs.

Assessments

Assessments took place at baseline (T0), 12 weeks (T1) and 24 weeks (T2). All assessments were done by a trained assessor (FJvdG) blinded for the treatment condition. Sociodemographics, disease-characteristics, past/current medication and Modified Rodnan Skin Score (18) were assessed at baseline.

Recording of individual treatments

All individual treatments by rheumatologists, physical therapists, occupational therapists, nurses, and social workers in both the intervention and control groups during the duration of the trial were recorded in the medical files by the treating rheumatologists and for patients in the intervention group also by the clinical nurse specialist.

Outcome measures of effectiveness

Body Functions

The Hand Mobility in Scleroderma (HAMIS) test consists of 9 items graded on a scale of 0-3, the final score ranges from 0 (normal function) to 27 (severe immobility). It was found to be a reliable instrument in evaluation of hand function in SSc (19) and longitudinal assessment of hand mobility in early SSc (20). An average value of the left and right hand was computed.

Grip-strength (kg) was measured with a Jamar dynamometer (JA Preston Corporation) (21). After testing twice, the highest score was registered. An average value of the grip-strength of the left and right hand was computed.

The maximal mouth opening (MMO) was measured with a digital caliper as the maximal interdental distance. Measurement of the MMO was used in several studies evaluating mouth function in SSc (16;22).

The 6-minute-walk-distance (6MWD) evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism (23). It reflects daily exercise and has good construct validity as demonstrated in patients with SSc and associated pulmonary arterial hypertension.

The maximum aerobic capacity (VO_{2max}) a standard exercise test on an electronically braked cycle ergo meter performed according to the ATS/ACCP Statement on Cardiopulmonary Exercise Testing (24). At baseline (forehead) pulse oximetry, blood pressure, heart rate and gas exchanges were recorded. Pulse-oximetry and heart rate were monitored during 1 min of rest, 2 min of unloaded cycling at 60 revolutions per minute followed by an increasing load to maximum tolerance, and 3 min of recovery. Each exercise test was supervised by a pulmonary physician [MKN]. Apart from the VO_{2max}, maximal load, heart rate and ventilation at maximal tolerated work rate were monitored.

The Checklist Individual Strength-20 (CIS-20) is a Dutch generic 20-item questionnaire measuring 4 dimensions of fatigue: fatigue, concentration, impaired motivation and impaired activity on a seven-point Likert scale (25). Higher scores indicate a higher degree of fatigue, more concentration problems, reduced motivation, and less activity. The CIS-20 was developed for patients with chronic fatigue syndrome, and has good psychometric properties (25).

Functional ability. The SSc Health Assessment Questionnaire (HAQ) is a 20-item questionnaire comprising eight domains of activities of daily living, with the final score ranging from 0 (no disability) to 3 (severe disability) and visual analog scales. The SSc HAQ score was calculated using the aids/devices. It has been found to be a reliable outcome measure for disease severity in SSc (26). In addition, a Dutch HAQ-translation demonstrated good psychometric properties (27).

Quality of life. The Short Form-36 (SF-36) is a generic measure of quality of life that can be converted into two summary scales: the physical component summary scale (PCS) and mental component summary scale, standardized to a score with a mean ± SD of 50 ± 10 in the general population. For this purpose, we used the scores from an age- and sex-matched, normative sample, drawn from a random sample of Dutch adults (n=1,742) (28) and factor score coefficients (29). The SF-36 has been found to be a reliable outcome measure for disease severity in SSc (26).

Statistical analysis. The target study sample size was based on the expected improvement of the 6MWD, HAQ and the PCS of the SF-36, since these outcomes are frequently used in rehabilitation studies aiming for improvement of exercise tolerance and functional status in patients with other chronic disease (30-34). At the time of this study design, no information on outcome parameters of other rehabilitation programs in SSc was available. In a non controlled study (35) a similar 12-week exercise program

for dermatomyositis patients resulted in a 30% improvement of a 7-minute-walk-distance (from 312 meter [range 81-422 to 404 meter [range 124-549). Assuming a 30% improvement in the intervention group and 0% in the control group, α=0.05 and β =0.20 (power of 0.80), 22 patients per group would be needed to detect this difference ($n = 7.85 \times 0.15[0.85] \times 2 / [0.3]^2$). A power calculation based on the PCSS gave similar results. In a study on a similar rehabilitation program in rheumatoid arthritis (RA) patients, a 22% improvement of the HAQ was seen (33). Assuming a 22% improvement in the intervention group and 0% in the control group, α=0.05 and power of 0.80, 28 patients per group would be needed to detect this difference ($n = 7.85 \times 0.11[0.78] \times 2 / [0.22]^2$). Based on an average of these calculations we aimed to enroll 50 patients in the study.

Data entry was performed using Microsoft Office Access 2003. All results were reported according to the Consolidated Standards of Reporting Trials Statement to Randomized Trials of Non-pharmalogic Treatment (36). Analysis was performed by the intention-to-treat principle.

Statistical analyses were executed using SPSS 16.0 software. Measures with a Gaussian distribution on histogram are expressed as the mean ± SD, measures with a non-Gaussian distribution as median and Inter Quartile Range (IQR; expressed as the net result of 75th -25th percentiles) or range. In case of more than 20% of missing data for one variable the group mean value for that variable would be imputed. Descriptive statistics were calculated for all variables, comparisons of baseline characteristics and numbers of patients using individual treatments were done by a Chi Square test, independent t-test, Mann Whitney U test or Fisher exact test where appropriate. The level of statistical significance (two sided) was set at *P* values less than 0.05.

In both the intervention and the control groups, the changes in the outcome measures between the baseline and 12 weeks assessments (Change 0-12 weeks) as well as between the baseline and 24 weeks assessments (Change 0-24 weeks) were assessed with a paired t-test. Comparison of the change scores between the intervention and control groups were done by performing analysis of covariance with correction for baseline values.

Results

Patient inclusion and characteristics. Ninety-one patients were considered to be potentially eligible for the study according to their medical records and were contacted (Figure 1).

Sixty patients were interested and took part in the further screening. Fifty-three patients (88%) met the inclusion criteria; 28 participants were randomly assigned to the multidisciplinary team care program, and 25 to the control group. The study was completed by 24 (86%) of 28 patients in the intervention group and by 23 (92%) of

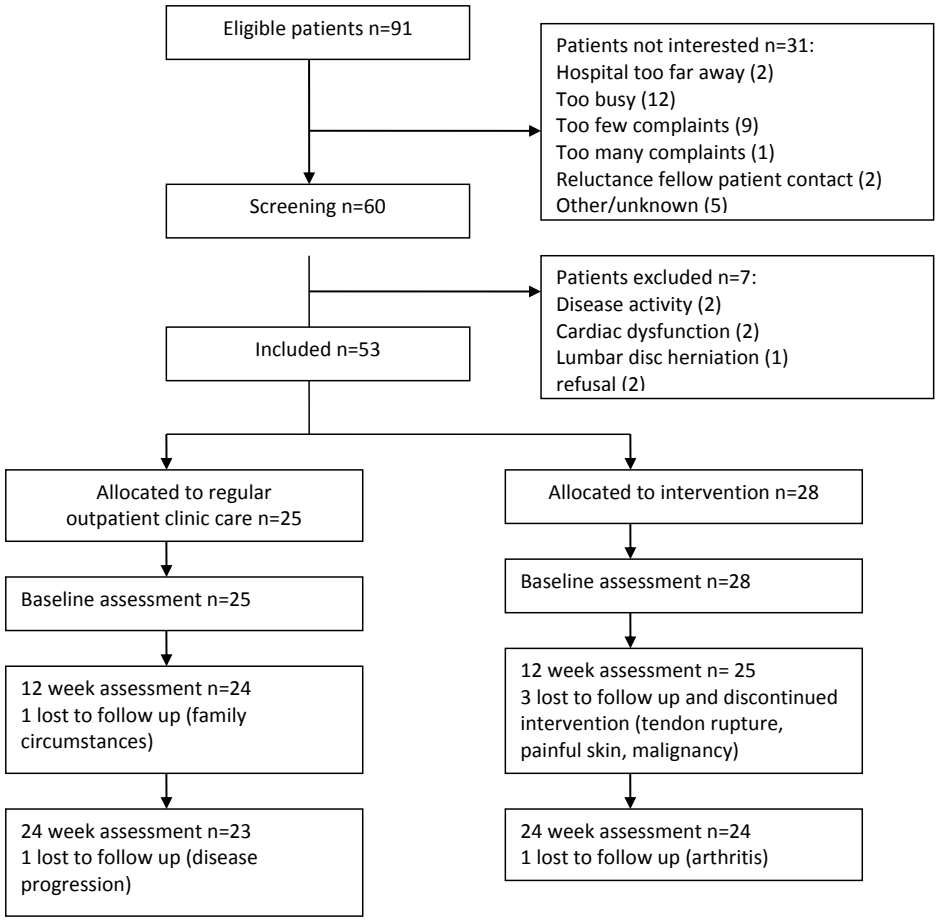

Figure 1: Flow diagram of a randomized comparison of a multidisciplinary treatment program with regular outpatient care in patients with SSc.

25 patients in the control group (p=0.671). Reasons for discontinuation of the study were family circumstances and disease progression in the control group, and tendon rupture, painful skin, malignancy and arthritis in the intervention group.
Table 1 shows the demographic and disease-characteristics of patients in the intervention and control groups. None of the differences between the two groups reached statistical significance.

Individual treatments in intervention and control groups.
Table 2 shows the numbers of patients receiving individual treatments provided by the rheumatologist and other rheumatology health professionals in both the intervention and the control groups. For the rheumatologist and all health professionals, significantly more patients in the intervention group received individual treatments.
Adverse effects and adherence to the multidisciplinary intervention.
Two patients in the intervention group had adverse effects related to the treatment program. One experienced a progressively painful skin in 3 weeks of participation, resulting in discontinuation of the program. An increased thickening or inflammation of the skin was not seen. The other patient suffered an Achilles tendon rupture during the circuit training in the second week. One patient discontinued the intervention prematurely because of an osteosarcoma requiring surgical intervention. During the bicycle training, six patients in the intervention group trained with a intensity lower then 60% of the specific maximum heart rate, because of pain diagnosis of osteoarthritis: n=4, exertion: n=2). Changes in usage of analgesics were not seen during the program for any of the patients in the intervention group.
Of the 25 patients completing the program, 20 (80%) attended 10 or more of both the 12 supervised group exercise (general) sessions and the 12 supervised group exercise (hand/mouth) sessions. For the supervised 21 patients (84 %) attended 10 or more of the 12 scheduled individual exercise sessions at the private practices. Twenty-one (84%) of the patients performed their exercise of hand and mouth on at least five days of the recommended six days per week. Twenty-three patients (92%) attended 5 or more of the 6 group educational sessions.

Endpoints of effectiveness
Less than 20% of the values were missing at any time point and the missing data were completely at random for all of the endpoints, so no imputation of data was employed. Table 3 shows the baseline values and change scores of all outcome measures. At 12 weeks the improvement of the grip-strength, MMO, 6MWD and HAQ was significantly greater in the intervention group than in
the control group. The changes of the other outcomes were comparable between the groups. At 24 weeks, this significance was sustained for the grip strength.

Table 1: Disease characteristics of 53 systemic sclerosis patients participating in a randomized, controlled trial evaluating the effectiveness of a multidisciplinary team care program as compared to usual care.

	Intervention group n=28	Control group n=25	P value*
Sex, Female No. (%)	19 (67.9)	21 (84.0)	0.297
Age, year, mean (SD)	53.9 (10.8)	51.7 (10.8)	0.459
Disease duration, year, median (IQR)	6.5 (8.2)	8.2 (10.5)	0.708
Disease subset diffuse SSc (%)	15 (53.6)	15 (60.0)	0.846
Onset Raynaud phenomenon, months, median (IQR)	8.6 (12.7)	10.3 (12.9)	0.694
MRSS‡ (0-51), mean (SD)	5.0 (4.0)	5.2 (6.2)	0.865
Auto-antibodies (% positive)			
ANA	23 (92.9)	23 (92.0)	1.000
Anti-Scl70	10 (35.7)	10 (40.0)	0.878
Anti-Centromere	3 (10.7)	5 (20.0)	0.335
ESR♦ mm/hr, median (IQR)	14.0 (19.0)	20.5 (30.0)	0.059
CRP◊, median (IQR)	3.0 (3.0)	5.0 (7.5)	0.159
Interstitial Lung Disease, no. (%)	13 (46.4)	12 (48.0)	1.000
Cardiac involvement, no (%)	2 (8)	5 (17.6)	0.426
FVC§, % predicted, mean (SD)	91.0 (21.9)	95.0 (21.1)	0.994
DLCO†, % predicted, mean (SD)	61.4 (17.5)	61.3 (18.1)	0.498
Current treatment, no (%)			
methotrexate	4 (14)	2 (8)	0.472
prednisone	4 (14)	1 (4)	0.201
azathioprine	2 (7)	2 (8)	0.632
Previous treatment no (%)			
cyclophosphamide	7 (25.0)	7 (28.0)	0.920
stemcell transplantation	6 (21.4)	4 (16.0)	0.472
methotrexate	8 (28.6)	9 (36.0)	0.831
prednisone	7 (25.0)	6 (24.0)	1.000

*Chi Square, student T test, Mann Whitney U test or Fisher exact test where appropriate; ‡Modified Rodnan Skin Score; ♦ ESR=erythrocyte sedimentation rate; ◊CRP=C-reactive protein; §FVC=Forced Vital Capacity; †DLCO=diffusing lung capacity of carbon monoxide.

Table 2. Numbers of patients receiving individual treatments provided by the rheumatologist and rheumatology health professionals during the 12-week intervention period, 12 weeks thereafter and the total period of 0-24 weeks.

Intervention Group (n=28)						**Control Group (n=25)**	**p-value #**
	Baseline	0-12 weeks	12-24 weeks	*0-24 weeks*	*0-24 weeks, initial assessment excluded*	0-24 weeks	
	Initial assessment	≥1 consultation	≥ 1 consultation	≥ 1 consultation	≥ 1 consultation	≥ 1 consultation	
Rheumatologist	28	21	18	28	26	17	0.030
Physical Therapist*	28	28*	28	28	28	10	0.000
Occupational Therapist	28	22	3	28	22	1	0.000
Social Worker	28	17	4	28	17	2	0.000
Clinical Nurse specialist	28	28	2	28	28	4	0.000

*All 28 patients in the intervention group received individual general exercise therapy (12 sessions) at a private practice during the intervention period of 0-12 weeks plus, if needed, individual physical therapy sessions at the clinic, depending on individual health status.#Comparisons (Chi-Square or Fisher exact tests) of numbers of patients receiving individual treatments in the intervention and control groups over 0-24 weeks (initial assessment of intervention group excluded).

Table 3. Endpoints of body functions, functional ability and quality of life in 53 patients with systemic sclerosis participating in a randomised controlled trial evaluating the effectiveness of a multidisciplinary team care program

		Baseline	p●	Change 00-12 weeks	p †	Change 00-24 weeks	p†
Body functions							
HAMIS, mean (SD)	I	6.8 (5.4)	0.449	**-1.2 (-2.2, -0.3)***	0.163	-1.3 (-2.7, 0.1)	**0.038**
	C	5.7 (3.9)		-0.2 (-1.1, 0.7)		0.7 (-0.5, 1.8)	
Grip strength (kg), mean (SD)	I	26.2 (12.4)	0.882	**2.2 (0.6, 3.8)***	**0.001**	2.1 (0, 4.1)	0.121
	C	26.7 (10.3)		**-1.8 (-3.4, -0.1)***		-0.3 (-2.7, 2.0)	
Mouth opening (mm) mean (SD)	I	36.5 (9.3)	0.632	**1.4 (-2.8, 0)***	**0.000**	1.4 (-0.3, 3.0)	**0.004**
	C	37.6 (6.6)		-0.9 (-0.5, 2.2)		-0.4 (-1.5, 0.7)	
Six MW test▼ (m) mean (SD)	I◊	499.9 (107.2)	0.472	**42.8 (22.1, 63.6)** *	**0.021**	**34.8 (7.9, 61.8)** *	0.280
	C‡	520.6 (94.2)		3.9 (-20.8, 28.5)		12.0 (-13.1, 37.1)	
O2 uptake¶ , mean (SD)	I	20.4 (5.1)	0.645	1.1 (-0.3, 2.6)	0.201	1.1 (-0.9, 3.2)	0.745
	C	21.1 (5.7)		-0.1 (-1.2, 1.0)		0.6 (-0.9, 2.1)	
CIS-20§ mean (SD)	I	74.2 (27.6)	0.172	**-13.4 (-20.9, -5.9)***	0.189	-7.8 (-16.3, 0.8)	0.429
	C	84.0 (18.5)		-7.9 (-19.6, 3.9)		-5.7 (-13.4, 2.1)	
Functional ability							
SSc-HAQ, mean (SD)	I	0.81 (0.66)	0.632	**-0.18 (-0.36, -0.01)** *	**0.025**	**-0.26 (-0.51, 0)***	0.255
	C	0.73 (0.46)		0.13 (-0.02, 0.27)		-0.1 (-0.24, 0)	
Quality of life							
SF-36 PCSS°, mean (SD)	I	41.3 (11.4)	0.251	2.1 (-1.5, 5.7)	0.074	-0.7 (-3.7, 2.4)	0.675
	C	37.6 (10.4)		-0.5 (-4.4, 3.4)		1.4 (-2.4, 5.1)	
SF-36 MCSS♦ mean (SD)	I	51.9 (7.5)	0.662	0 (-2.9, 2.9)	0.906	1.9 (-1.2, 5.0)	0.677
	C	50.9 (7.4)		0.6 (-3.2, 4.3)		1.6 (-2.3, 5.5)	
VAS Pain (mm), mean (SD)	I	27.0 (27.7)	0.642	-5.7 (-14.2, 2.7)	0.053	-2.1 (-11.2,7.1)	0.465
	C	30.6 (25.5)		5.9 (-5.0, 16.8)		1.2 (-11.5, 13.9)	

●baseline in mean (SD); value C and I compared; † multiple linear regression comparison of Δ between C and I; ▼Six MW test=six minute walk test; ◊I=patients in the intervention group; ‡C=patients in the control group; Δ = mean difference in change with 95% confidence interval; *=p<0.05; °PCSS=Physical Component Summery Scale; ¶maximal oxygen uptake during bicycle exercise test; □VAS= visual analogue scale; ♦MCSS=Mental Component Summary Scale; §CIS-20=Checklist Individual Strength

Discussion

This proof of concept randomized trial shows that a 12-week day patient multidisciplinary rehabilitation program resulted in a greater improvement of grip-strength, mouth opening, 6MWD and the HAQ than regular outpatient care. Although differences were still present at 24 weeks, the significance of most of them was not sustained. No differences were seen for VO_{2max}, HAMIS, CIS-20, SF 36 and visual analog scale for pain. The results of previous evaluations of comprehensive rehabilitation programs in SSc are similar to our study with respect to significant improvements of mouth opening (10;11;16), hand function (9;10) and overall functional ability (10) in the intervention group. The mean increase of mouth opening in our patients was considerably less then in two other studies (10;16). However, compared with these studies, the patients in our study had a less impairment: 8% had a normal mouth opening (>50.0 mm), and 36% had a mouth opening >40.0 mm (22), making an overall group improvement more difficult to achieve. The hand exercises in our program resulted in a moderate decrease of the HAMIS as compared to 20 patients completing a 9 week rehabilitative treatment (mean ±SD 6.8 to 5.6 (±1.2) versus 11.4 to 7.0 ± 4.4) (17). This difference may also be explained by a lower level of baseline hand disability in our patients, and the different type of intervention.

In both previous studies (9;10) an improvement of quality of life was seen. Although our study showed a greater improvement of overall physical health in the intervention group as compared to the control group, the difference did not reach significance. The significant improvement of the 6MWD and the HAQ but not of the SF-36 PCS scale is suggests that these outcomes may reflect different dimensions of physical functioning. This is in line with a study by Khanna et al (26) on the responsiveness of change the HAQ-DI compared with the SF-36 in patients with dcSSc. The HAQ-DI had a larger magnitude of responsiveness if clinical measures were considered, while the SF-36 had a larger magnitude of responsiveness in overall disease activity (patient and physician global assessment). On the other hand, Antonioli (9) found a statically significant improvement of both of the subscales after a 2-week rehabilitation program. In the absence of a gold standard to measure the effect of rehabilitation interventions in SSc, we employed different endpoint measures. In this respect, this trial should be considered as a proof of concept study with its results warranting further research.

Comparisons among studies are hampered by a number of differences. With respect to the intervention, previous studies had a strong focus on physical therapy interventions (9;10;14;17). Maddali Bongi (10) used a 9-week tailored rehabilitation program, with education, mostly passive treatment of hand and face for one hour twice a week and a general exercise program for one hour once week. Antonioli's (9) 2-week program with exercise therapy and physical modalities had a shorter duration, but was followed by at-home exercises. In the present study more health care professionals were involved

(including occupational therapists, clinical nurse specialists and social workers) and a greater variety of treatments was provided, including group education and individual interventions tailored to patients' needs. A similar multidisciplinary team care model as employed in the present study was found to be effective in patients with RA (33;37). Second, the two previous studies (10, 11) used other outcome measures. Third, in neither of the two previous studies a direct comparison was made between the intervention and the control groups, so that the changes reported can not be interpreted as treatment effects. Finally, there were differences in the baseline characteristics of the patients. In general, it can be assumed that in patients with lower levels of impairment an improvement of disability is more difficult to achieve. In SSc a classification of the HAQ has been proposed into no-to-mild disability (0.00–1.00), moderate disability (1.01–2.00) and severe disability (2.01-3.00) (38). Using this classification, participants in our study (HAQ score of 0.81) and Antonioli et al (9) (HAQ score of 0.63) had a mild disability, and in the study by Maddali Bongi, participants had moderate disability (HAQ score of 1.2).

Exercise performance in SSc may be limited because of circulatory, pulmonary or joint–muscle impairment (39). There are only two studies available on exercises aiming to improve exercise tolerance in SSc. A two-week rehabilitation including lower extremity exercises showed no improvement of the 6MWD (9), whereas our program resulted in a mean improvement of 42.8m of the 6MWD (8.5%). The considerably longer duration of our supervised training may be a reason for the difference. An eight-week program with moderate intensity aerobic exercise (14) resulted in a significant improvement of Vo_{2max} in seven SSc patients, whereas in our study no improvement of the Vo_{2max} was seen. This discrepancy may be due to the fact that almost half of the patients in our study had interstitial lung disease (ILD); an improved 6MWD, but not Vo_{2max} was found after physical training for people with ILD (40). Unfortunately the number of patients participating in this study did not permit subgroup analysis for patients without ILD. The benefits of dynamic exercise have been documented in conditions such as dermatomyositis and polymyositis (41), SLE (42) and RA (43). Moreover, it is considered appropriate to include patients with ILD in pulmonary rehabilitation (34), despite the absence of improved Vo_{2max}.

Although the improvement of most outcomes was still present at 24 weeks, the significance was not sustained. This is in line with literature rehabilitation outcomes in SSc (10), ILD (34) and RA (43), underlining the importance of continued exercises and physical activity incorporated in patient's daily life. This is substantiated by Antonioli's study (9); the 2-week program of individual sessions was followed by home exercises, patients were asked to keep a dairy of activities, and patients were regularly asked for compliance, resulting in an increasing improvement of quality of life as measured by the SF-36 after 2 and 4 months. These results suggest that by promoting lifelong exercises and physical activity as a part of the standard treatment in SSc health care

providers may contribute to sustained improvement of physical functioning and quality of life.

The dynamic exercise program as employed in the present study appeared to be safe and well tolerated by the majority of SSc-patients. However, considering the rupture of an Achilles tendon in one SSc-patient despite stretching in advance, extra attention should be paid to warming up. One patient ended participation because of painful skin, without visible skin inflammation. Whether this painfulness was due to increased inflammation is unclear. Increased anti-interleukin-6 and circulating leucocytes were demonstrated in SSc patients after cardiopulmonary exercise testing (44). In healthy subjects, participation in regular exercise (i.e.,training) can reduce basal or resting levels of many inflammatory markers (45). In RA patients, 12 weeks of progressive resistance exercises did not lead to the biologically important alterations in immune response after an acute bout of exercise as compared to healthy controls (46). Finally, no signs of increased inflammation were seen in a muscle biopsy sample in nine patients with chronic dermatomyositis and polymyositis after 7 weeks of intensive resistance training (41).

Concerning the educational part of the program, similar programs have been described (12;13) and were found to be well appreciated by SSc patients. The effectiveness of patient education on coping, depression or illness perception has not yet been established. Our program did not result in improvement of mental status, probably because in our study patients had impairment of physical rather then mental health. A number of studies however have described a high prevalence of depressive symptoms (6), pain (47) and body image dissatisfaction in SSc (48). In RA tailored cognitive-behavioral therapy only offered to patients with a high psychosocial risk profile was effective in reducing depression and fatigue (49). Cognitive-behavioral or other psychosocial interventions has not yet been evaluated in SSc, but they could gain in effectiveness if offered to patients with a high risk profile.

Our study has several limitations. First, the sample size did not permit subgroup analysis to identify patients with the greatest benefits. Mugii (15) illustrated that early dcSSc patients would benefit more from ROM exercises than patients in later stages. In our study, most of the dcSSc patients participating had non-active SSc with longer disease duration. As previously discussed, it is likely that ILD also determines outcome in rehabilitation interventions. Secondly, our program focused on improving physical functioning more than on mental functioning. Thirdly, in case of a multidisciplinary approach, it is difficult to establish which component of the team care contributes most to the treatment effect. More knowledge on the effects of single techniques can be obtained by comparing different rehabilitation strategies.

Acknowledgment

We thank the patients for their efforts and cooperation, the multidisciplinary team of Rheumatology Clinic Sole Mio for developing the day care program and Atos Medical, Zoetermeer, The Netherlands, for kindly providing a Therabite® device for a number of patients taking part in the intervention.

Appendix: Content of a 12-week multidisciplinary team care program for Systemic Sclerosis patients provided in a day care setting

	Content	Location	Frequency
STANDARDIZED TREATMENT			
Exercises			
• supervised group exercises (general)	Warming up (10 minutes) Bicycle training (20 minutes) • aiming at a minimum of 60% of the age-specific maximal heart rate, adaptation if necessary Exercise circuit (20 minutes) • 8-10 exercises to improve cardio-pulmonary fitness, muscle strength/endurance and joint mobility, repeated 8-15 times if possible Sport or game (20 minutes); ball games/badminton Cooling down (10 minutes)	Hospital	2 hours/week
• supervised group exercises (hand/ mouth)	Hand exercises • 8 consecutive Range of Motion (ROM) exercises of the metacarpo-phalangeal and proximal interphalangeal joints (each exercise comprising of 1 active-assisted motion followed by 3 active motions; 1 serie of 3 repetitions)	Hospital	15 minutes/ week
	Mouth exercises • dynamic mouth stretchings; opening the mouth as wide as possible with help of a Therabite® stretching device (Atos Medical; Zoetermeer, The Netherlands) with intermitting variations of effort (1 repetition).. • static mouth stretching; maintaining a maximal mouth opening with maximum effort and help of a Therabite® stretching device for 60 seconds, followed by five dynamic mouth stretching (three repetions in one series)	Hospital	15 minutes/ week
• supervised individual (general)	5 consecutive fitness exercises aiming at a minimum of 60% of the age-specific maximal heart rate, adaptation if necessary. Each exercise 6 minutes with 4 minutes breaks between the exercises.	Private practice	1 hour/week
• home based individual (hand/ mouth)	Hand exercises as in supervised group session	Patient's home	10 minutes/ day, 6 days/ week
	Mouth exercise as in supervised group session	Patient's home	5 minutes/day 6 days/week
Education			
• supervised group meetings	Power point presentation by a health care provider followed by a group discussion. Subjects: (1) information on the disease and medication; (2) skills for coping with pain, disfigurement and disability; (3) skin care; (4) oral hygiene; (5) sexuality; (6) food and diet. Also standardized written information materials (leaflets, books, references to websites)	Hospital	1 hour / 2 weeks
INDIVIDUAL TREATMENTS			
	Team members: Occupational therapist, social worker, clinical nurse specialist, physical therapist, rheumatologist • standardized initial assessment by all team members (5 x 45 minutes) with individual goal setting on the level of body functions and structures, daily activities, societal participation and environmental and personal factors in co-operation with the patient; Standardized evaluation of goal attainment at 3-weekly multidisciplinary team conferences • at least one consultation with the rheumatologist and three consultations with the clinical nurse specialist during the program (apart from the initial assessment); additional individual consultations with the rheumatologist, the clinical nurse specialist or other team members or additional medical specialists depending on the individual patient's health status.	Hospital	

Reference List

(1) LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Jr. et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988; 15(2):202-5.

(2) Medsger TA, Jr. 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(2):255-73, vi.

(3) Hudson M, Thombs BD, Steele R, Panopalis P, Newton E, Baron M. Quality of life in patients with systemic sclerosis compared to the general population and patients with other chronic conditions. J Rheumatol 2009; 36(4):768-72.

(4) Pope JE. Musculoskeletal involvement in scleroderma. Rheum Dis Clin North Am 2003; 29(2):391-408.

(5) Denton CP, Black CM. Scleroderma--clinical and pathological advances. Best Pract Res Clin Rheumatol 2004; 18(3):271-90.

(6) Thombs BD, Hudson M, Taillefer SS, Baron M. Prevalence and clinical correlates of symptoms of depression in patients with systemic sclerosis. Arthritis Rheum 2008; 59(4):504-9.

(7) Vliet Vlieland TP. Multidisciplinary team care and outcomes in rheumatoid arthritis. Curr Opin Rheumatol 2004; 16(2):153-6.

(8) Poole JL. Musculoskeletal rehabilitation in the person with scleroderma. Curr Opin Rheumatol 2010; 22(2):205-12.

(9) Antonioli CM, Bua G, Frige A, Prandini K, Radici S, Scarsi M et al. An individualized rehabilitation program in patients with systemic sclerosis may improve quality of life and hand mobility. Clin Rheumatol 2009; 28(2):159-65.

(10) Maddali Bongi S., Del Rosso A., Galluccio F, Tai G, Sigismondi F, Passalacqua M et al. Efficacy of a tailored rehabilitation program for systemic sclerosis. Clin Exp Rheumatol 2009; 27(3 Suppl 54):44-50.

(11) Maddali-Bongi S, Landi G, Galluccio F, Del RA, Miniati I, Conforti ML et al. The rehabilitation of facial involvement in systemic sclerosis: efficacy of the combination of connective tissue massage, Kabat's technique and kinesitherapy: a randomized controlled trial. Rheumatol Int 2010.

(12) Brown SJ, Somerset ME, McCabe CS, McHugh NJ. The impact of group education on participants' management of their disease in lupus and scleroderma. Musculoskeletal Care 2004; 2(4):207-17.

(13) Samuelson UK, Ahlmen EM. Development and evaluation of a patient education program for persons with systemic sclerosis (scleroderma). Arthritis Care Res 2000; 13(3):141-8.

(14) Oliveira NC, Dos Santos Sabbag LM, de Sa Pinto AL, Borges CL, Lima FR. Aerobic Exercise is Safe and Effective in Systemic Sclerosis. Int J Sports Med 2009.

(15) Mugii N, Hasegawa M, Matsushita T, Kondo M, Orito H, Yanaba K et al. The efficacy of self-administered stretching for finger joint motion in Japanese patients with systemic sclerosis. J Rheumatol 2006; 33(8):1586-92.

(16) Pizzo G, Scardina GA, Messina P. Effects of a nonsurgical exercise program on the decreased mouth opening in patients with systemic scleroderma. Clin Oral Investig 2003; 7(3):175-8.

(17) Maddali Bongi SM, Del Rosso A., Galluccio F, Sigismondi F, Miniati I, Conforti ML et al. Efficacy of connective tissue massage and Mc Mennell joint manipulation in the rehabilitative treatment of the hands in systemic sclerosis. Clin Rheumatol 2009; 28(10):1167-73.

(18) Clements P, Lachenbruch P, Siebold J, White B, Weiner S, Martin R et al. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol 1995; 22(7):1281-5.

(19) Sandqvist G, Eklund M. Hand Mobility in Scleroderma (HAMIS) test: the reliability of a novel hand function test. Arthritis Care Res 2000; 13(6):369-74.

(20) Sandqvist G, Hesselstrand R, Eberhardt K. A longitudinal follow-up of hand involvement and activities of daily living in early systemic sclerosis. Scand J Rheumatol 2009;1-7.

(21) Schmidt RT, Toews JV. Grip strength as measured by the Jamar dynamometer. Arch Phys Med Rehabil 1970; 51(6):321-7.

(22) Naylor WP, Douglass CW, Mix E. The nonsurgical treatment of microstomia in scleroderma: a pilot study. Oral Surg Oral Med Oral Pathol 1984; 57(5):508-11.

(23) ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111-7.

(24) ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003; 167(2):211-77.

(25) Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38(5):383-92.

(26) Khanna D, Furst DE, Clements PJ, Park GS, Hays RD, Yoon J et al. Responsiveness of the SF-36 and the Health Assessment Questionnaire Disability Index in a systemic sclerosis clinical trial. J Rheumatol 2005; 32(5):832-40.

(27) Boers M, Jacobs JW, van Vliet Vlieland TP, van Riel PL. Consensus Dutch health assessment questionnaire. Ann Rheum Dis 2007; 66(1):132-3.

(28) Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998; 51(11):1055-68.

(29) Ware JE jr, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey: manual and interpretation guide. Boston: The Health Institute, New England Medical Center; 1993.

(30) Merkel PA, Clements PJ, Reveille JD, Suarez-Almazor ME, Valentini G, Furst DE. Current status of outcome measure development for clinical trials in systemic sclerosis. Report from OMERACT 6. J Rheumatol 2003; 30(7):1630-47.

(31) Hwang R, Marwick T. Efficacy of home-based exercise programmes for people with chronic heart failure: a meta-analysis. Eur J Cardiovasc Prev Rehabil 2009; 16(5):527-35.

(32) Spencer LM, Alison JA, McKeough ZJ. Maintaining benefits following pulmonary rehabilitation: a randomised controlled trial. Eur Respir J 2009.

(33) Tijhuis GJ, Zwinderman AH, Hazes JM, Van Den Hout WB, Breedveld FC, Vliet Vlieland TP. A randomized comparison of care provided by a clinical nurse specialist, an inpatient team, and a day patient team in rheumatoid arthritis. Arthritis Rheum 2002; 47(5):525-31.

(34) Holland A, Hill C. Physical training for interstitial lung disease. Cochrane Database Syst Rev 2008;(4):CD006322.

(35) Alexanderson H, Stenstrom CH, Lundberg I. Safety of a home exercise programme in patients with polymyositis and dermatomyositis: a pilot study. Rheumatology (Oxford) 1999; 38(7):608-11.

(36) Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann Intern Med 2008; 148(4):295-309.

(37) O'Donnell S, Li LC, King J, Lauzon C, Finn H, Vliet Vlieland TP. Development of a framework for reporting health service models for managing rheumatoid arthritis. Clin Rheumatol 2010; 29(2):151-65.

(38) Khanna D, Clements PJ, Postlethwaite AE, Furst DE. Does incorporation of aids and devices make a difference in the score of the health assessment questionnaire-disability index? Analysis from a scleroderma clinical trial. J Rheumatol 2008; 35(3):466-8.

(39) Blom-Bulow B, Jonson B, Bauer K. Factors limiting exercise performance in progressive systemic sclerosis. Semin Arthritis Rheum 1983; 13(2):174-81.
(40) Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax 2008; 63(6):549-54.
(41) Alexanderson H, Dastmalchi M, Esbjornsson-Liljedahl M, Opava CH, Lundberg IE. Benefits of intensive resistance training in patients with chronic polymyositis or dermatomyositis. Arthritis Rheum 2007; 57(5):768-77.
(42) Carvalho MR, Sato EI, Tebexreni AS, Heidecher RT, Schenkman S, Neto TL. Effects of supervised cardiovascular training program on exercise tolerance, aerobic capacity, and quality of life in patients with systemic lupus erythematosus. Arthritis Rheum 2005; 53(6):838-44.
(43) Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, Schoones J, Van den Ende EC. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. Cochrane Database Syst Rev 2009;(4):CD006853.
(44) Hargardottir H, van Helvoort HA, Vonk MC, van den Hoogen FH, Dekhuijzen PN, Heijdra YF. Exercise in systemic sclerosis intensifies systemic inflammation and oxidative stress. Scand J Rheumatol 2010; 39(1):63-70.
(45) King DE, Carek P, Mainous AG, III, Pearson WS. Inflammatory markers and exercise: differences related to exercise type. Med Sci Sports Exerc 2003; 35(4):575-81.
(46) Rall LC, Roubenoff R, Cannon JG, Abad LW, Dinarello CA, Meydani SN. Effects of progressive resistance training on immune response in aging and chronic inflammation. Med Sci Sports Exerc 1996; 28(11):1356-65.
(47) Benrud-Larson LM, Haythornthwaite JA, Heinberg LJ, Boling C, Reed J, White B et al. The impact of pain and symptoms of depression in scleroderma. Pain 2002; 95(3):267-75.
(48) Benrud-Larson LM, Heinberg LJ, Boling C, Reed J, White B, Wigley FM et al. Body image dissatisfaction among women with scleroderma: extent and relationship to psychosocial function. Health Psychol 2003; 22(2):130-9.
(49) Evers AW, Kraaimaat FW, van Riel PL, de Jong AJ. Tailored cognitive-behavioral therapy in early rheumatoid arthritis for patients at risk: a randomized controlled trial. Pain 2002; 100(1-2):141-53.

CHAPTER 9

Summary

Chapter 1 is a general introduction including the definition of SSc, epidemiology, disease manifestations in terms of body function and structures and activities and participation, measurement instruments and an overview of both pharmacological and non-pharmacological treatment.

In ***Chapter 2*** myocardial function in SSc patients was assessed by echocardiography using speckle tracking strain analysis, and the relationship of this technique with functional capacity and ventricular arrhythmias was investigated. In 104 SSc patients cardiopulmonary exercise testing, 24-hour electrocardiography (EKG) Holter monitoring, and trans-thoracic echocardiography was performed. For comparison, 37 matched healthy controls were included. No significant difference between patients and controls was seen in ventricular volumes or left ventricular ejection fraction (LVEF). However, estimated pulmonary arterial systolic pressure (PASP) was significantly higher and diastolic function, global longitudinal and circumferential strains were significantly more impaired in SSc patients as compared to controls. Global longitudinal and circumferential strains demonstrated a correlation with cardiopulmonary exercise capacity as measured by the peak oxygen uptake (VO2), and multivariate analysis confirmed the independent association of each strain measure with the peak VO2. Moreover, compared to SSc patients with normal results on ECG Holter monitoring, SSc patients with abnormal results showed impaired global longitudinal and circumferential strain, and each strain measure was independently associated with abnormal Holter findings.

A negative impact of SSc on sexual function in men with SSc has been established previously. However studies on sexuality in women with SSc were are scarce until recently. In ***Chapter 3***, a cross-sectional study aimed to compare sexual functioning and distress in 37 women with SSc with those of 37 healthy controls and furthermore to assess the association between sexual function and disease characteristics. Validated questionnaires to evaluate sexual complaints included the Female Sexual Function Index (FSFI), Female Sexual Distress Scale (FSDS). It was found that women with SSc reported significantly more impaired sexual functioning and more sexual distress then healthy controls. Impaired sexual function was established in 70% of the patients, increased sexual distress in 57%, whereas 47% of the 37 patients would be considered to have sexual dysfunction (defined as both impaired sexual function plus high levels of sexual distress). More marital dissatisfaction and longer disease duration was seen in patients with more impaired sexual function. The usage of antidepressants, more depressive symptoms, and longer disease duration were statistically significantly associated with more sexual distress.
Multivariate analyses indicated that marital distress was the only variable significantly associated with low sexual function in patients with SSc, whereas depression was

the only variable significantly associated with sexual distress. The same pattern of associations was found in the healthy control group.
Six patients (16%) with SSc reported a need to talk to someone about current sexual problems, none of the patients mentioned their rheumatologist as a care provider in whom they would confide, and only 1 mentioned her general practitioner. It was concluded that in daily practice, inquiring about sexuality and screening for depressive symptoms is indicated in every patient with SSc, irrespective of their clinical characteristics.

In a **comment on Chapter 3**, Knafo et al argued that they felt routine inquiry about sexuality to be inappropriate. Their concerns included the low number of patients reporting a need to talk to someone about current sexual problems, and the need for further investigation of predictors of sexual impairment with sufficient power to detect potential upstream factors. The comment concluded that before health providers can be asked to reach beyond their level of comfort and training to address sexual issues, there's a need to provide them with a way to do so effectively. Moreover, clear patient benefit and effective interventions were proposed as conditions for active inquiry about sexuality. Knafo et al suggested the provision of general information by pamphlet as an alternative strategy to normalize the subject and facilitate discussion with a health professional.
In ***a response***, it was clarified that the low percentage of patients indicating a need to talk about possible sexual problems concerned the whole group and not to the subgroup of patients indicating sexual impairment. The justification for the simple question by a rheumatologist "do you experience problems in sexual activity?" is found in several arguments. First, in other chronic impairment it has been recognized that dealing with sexual problems should be addressed in medical rehabilitation. Second, the reluctance of both health professionals as well as patients to discuss sexuality is known; relying on a patient's initiative to discus problems in sexuality leads to the risk of avoidance of the subject. Third, considering the frequently mentioned SSc specific complaints it is very likely that a considerable number of female patients may benefit from simple health interventions as vaginal lubricants, medication advice or referral to another specialist. However, it was acknowledged that an important condition for discussing matters of sexuality is a health professional that is comfortable with the subject. Clearly there is a need for improvement of competences in this direction.

In ***Chapter 4*** the French-generic Mouth Handicap in Systemic Sclerosis (MHISS) questionnaire, evaluating mouth-opening restriction, dryness and esthetic concerns was translated , field-tested among 16 systemic sclerosis (SSc) patients and adapted into Dutch language. The validity of the Dutch MHISS was assessed by determining associations with measures of overall functioning (Health Assessment Questionnaire

(HAQ)), maximum mouth opening (MMO, in millimeter), subjective xerostomia (visual analog scale), and objective xerostomia (Saxon test) in 52 SSc patients. Dutch MHISS scores differed significantly between patients with high and low disability levels (HAQ, MMO, and subjective and objective xerostomia divided according to the median; paired t test). Spearman rank correlations with HAQ (r=0.60, p=0), MMO (r=-0.52, p=0), and subjective xerostomia (r=0.54, p=0.) were moderate; correlation with objective xerostomia did not reach statistical significance. Internal consistency was adequate as expressed by a Cronbach's alpha of 0.86. Test-retest reliability was established by an intraclass correlation coefficient (ICC) of 0.94. It was concluded that the Dutch version of the MHISS demonstrates good psychometric properties and is useful in assessing mouth disability in SSc patients.

In ***Chapter 5*** the validity and responsiveness of the Michigan Hand Questionnaire (MHQ) in SSc patients was assessed. The MHQ contains 57 items and 6 domains: function, activities of daily living, pain, work, aesthetics, and satisfaction. Data were gathered in connection with a randomized, controlled trial comparing the effectiveness of a 12-week multidisciplinary team care programme (including a hand function treatment module) with regular care. All fifty-three patients (28 intervention group and 25 control group) completed the MHQ at baseline and after 12 weeks. Other measures included the HAQ (Health Assessment Questionnaire), Hand Mobility in Scleroderma (HAMIS), Sequential Occupational Dexterity Assessment (SODA), grip strength, pinch grip and Modified Rodnan Skin Score (MRSS). Validity was determined by computing Spearman correlation coefficients between the baseline MHQ total score and subscales and other measures of (hand) disability. Responsiveness in the intervention group was evaluated by the standardized response mean (SRM), effect size (ES), and responsiveness ratio (RR). In addition, pooled ES for the difference between the two groups were computed. Significant correlations were seen between the MHQ total score and the HAQ (r=-0.62), HAMIS (r=-0.54), SODA (r=0.47), SODA Pain (r=0.32) and MRSS (r=0.46). The ES of the MHQ total score within the intervention group was 0.49, which was larger than those of all other outcome measures. Similar results were obtained for the SRM and RR. The pooled ES of the difference between intervention and control groups for the MHQ total score was 0.86. It was concluded that the MHQ demonstrated adequate validity and responsiveness in patients with SSc.

The objective of ***Chapter 6*** was to describe work status and factors associated with work disability (WD) in SSc patients based on a systematic review of literature available from 1990 to 2011. Clinical studies concerning SSc patients, data on work status and/or factors associated with WD. Twelve clinical studies containing quantitative information on work status in SSc patients and/or factors associated WD were selected, including 2.758 SSc patients. The methodological quality was evaluated in three quality aspects

(selection bias, information bias and statistical analysis bias) and was found high in 1/12 study. Employment rates varied between 11% and 82% after an average disease duration ranging from 2.5 to 14 years. There was moderate evidence for an association between more functional disability, more disease specific symptoms and worse quality of life on one side and presence of WD on the other. There was moderate evidence for the absence of an association between WD and age, sex and disease subset. Inconsistent evidence was seen for an association between WD and education and disease duration. It was concluded that WD is a major consequence of the disease in patients with SSc and is associated with more functional disability, more disease specific symptoms and worse quality of life. This emphasizes the need for research into interventions to prevent or reduce WD in patients with SSc, especially in those with a worse health status.

The aim of **Chapter 7** was to explore health care and information needs of SSc patients and the extent the patients' needs were met by current health care services delivery. Also, the association between needs and patient characteristics was studied. For this purpose a questionnaire was sent to 77 SSc-outpatients, comprising 27 items on health care needs within the domains physical, psychological, social support, employment/ daily activities or other health problems and 13 items on information needs. Also, the patients' preferences regarding the provision of health care services and information were listed. Sixty-four of seventy-seven patients (83%) returned the questionnaire. Twenty-seven patients (42%) reported one or more unmet health care needs, with the highest proportions of patients with unmet needs seen in the physical (30%) and psychological (20%) domains. The highest percentages of patients with information needs were observed for medical subjects (20-28%). Worse mental functioning was associated with a higher unmet health care need score, whereas worse physical functioning and a diagnosis of diffuse SSc were associated with higher information need score. A yearly, standardized multidisciplinary assessment program was most frequently mentioned as a preferred, but not yet existing, health care model (59%) and the rheumatologist as a preferred source of information supply (75%).

In ***Chapter 8*** a randomized controlled trial is described, evaluating the safety and effectiveness of a 12 week multidisciplinary team care program in SSc patients by comparison with usual outpatient care. The team care program was provided by the Rheumatology Ambulatory department of the Leiden University Medical Centre, with a frequence of one day per week and a total duration of 12 weeks. It consisted of:

a) Group sessions compromising general exercises, hand/mouth exercises, educational sessions

b) Individual treatments by the rheumatologist, occupational therapist, a physical therapist, a social worker, and a clinical nurse depending on the patients' individual needs.

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c) Individual supervised exercises provided by a physical therapist near their own home in a private practice once a week and a home-based exercise program on at least 6 days per week.

Outcome measures included the Hand Mobility in Scleroderma (HAMIS) test, grip strength, maximal mouth opening (MMO), 6-minute walk distance (6MWD), maximum aerobic capacity (VO2max), Checklist Individual Strength 20 (CIS-20), SSc Health Assessment Questionnaire (HAQ), and Short Form 36 (SF-36), assessed at 0, 12, and 24 weeks. Statistical comparisons of change scores were done by analysis of covariance.

Twenty-eight patients were assigned to the intervention group (mean age 53.9 years, 15 of 28 with diffuse SSc) and 25 were assigned to the control group (mean age 51.7 years, 15 of 25 with diffuse SSc). Twenty-five patients (89%) in the intervention group completed the treatment program. At 12 weeks, there was a significantly greater improvement in grip strength (2.2 versus -1.8 kg; $P < 0.001$), MMO (1.4 versus -0.9 mm; $P= 0.011$), 6MWD (42.8 versus 3.9 meters; $P = 0.021$), and HAQ score (-0.18 versus 0.13; $P= 0.025$) in the intervention group, whereas differences for the other outcome measures did not reach statistical significance. At 24 weeks, the effect on MMO persisted. It was concluded that in SSc patients a 12-week multidisciplinary day patient treatment program was more effective than regular outpatient care with respect to 6MWD, grip strength, MMO, and HAQ score, but not for VO2max, HAMIS test, CIS-20, SF-36, and visual analog scale for pain.

Discussion

Aims of this thesis were: to acquire more insight into the impact of SSc on a number of aspects related to the ICF chapters as well as into the patients' needs regarding information and health care in these areas; to examine the clinical and scientific value of a number of relevant disease outcome measures; and to evaluate the safety and effectiveness of a multidisciplinary rehabilitation program for patients with SSc. For this purpose cross sectional studies, a randomized controlled trial and a systematic review were performed. Two assessment methods, the Michigan Hand Questionnaires and the Mouth Handicap in Systemic Sclerosis questionnaire, were found to be valuable instruments to assess limitations in mouth and hand function. Also, a considerable impact of SSc on cardiac function, sexuality and work status was established, and despite relatively high health care usage, unmet needs related to health care provision were demonstrated in SSc patients. A multidisciplinary team care program which was developed to meet a part of these needs, proved to be effective in improving hand, mouth and global disability and mobility.

General methodological issues

A limitation of the studies presented in this thesis is that the majority of the patients concerned a selected group; for chapters 3 and 5 patients were recruited in the Leiden University Medical Center (LUMC), a specialized hospital for SSc care. For the studies described in chapters 2, 6, 7 and 8 patients were mainly recruited in the LUMC, and a small number of them were referred by rheumatologists working in general hospitals in the region. Because of this, selection bias can not be ignored; patients may have been referred to the academic hospital because of SSc complications or active disease and subsequent need of intensive immune modulatory treatment, resulting in a cohort of patients with relatively active or more complicated disease. However, a number of the patients in the studies included in this thesis had participated in the ASTIS trial (Autologous Stem Cell Transplantation International Scleroderma) a multi-center, prospective randomized study comparing autologous hematopoietic stem cell transplantation with intravenous pulse therapy cyclophosphamide treatment. This study included 25 LUMC patients with severe SSc. A considerable number of these patients achieved stable disease, in most of them skin fibrosis improved.

It is unclear to what extent characteristics differ between patients visiting hospitals specialized for SSc care and hospitals with general rheumatology departments. It may seem likely that in smaller hospitals a greater percentage of patients with limited subtype SSc is monitored, however this needs further study. Larger recruitment of mild-to-moderate clinical variants, which better reflect the entire SSc spectrum may influence the results.

In conclusion, due to probable selection bias in a number of the studies in this thesis, generalizability of the results is limited.

Part I: Body function and structure

Left ventricular systolic dysfunction

Once myocardial involvement is clinically evident, it is recognized as a poor prognostic factor in SSc patients (1). In order to improve long term outcome in SSc patients with primary myocardial involvement, it is important to identify those patients without overt clinical signs, but at high risk of cardiac deterioration. The purpose of screening and early detection is to identify mildly symptomatic patients, as well as those with pre-clinical disease in order to prevent or delay progression of disease through early treatment (2). SSc myocardial disease is a challenging subject for research. Vasodilators, such as calcium channel blockers and angiotensin converting enzyme inhibitors, have shown tot improve both myocardial perfusion and function abnormalities (3). Moreover, observational data suggest a role for calcium channel blockers in prevention of LV systolic dysfunction (4).

Screening for subclinical cardiac disease may contribute to the identification of high risk patients, however, unlike ILD and PAH, there are fewer data on optimal screening for direct cardiac involvement in SSc. Important questions remain that need to be addressed, such as; which abnormalities on cardiac screening tests are associated with functional limitation and/or adverse outcomes? Does treatment of SSc patients with asymptomatic cardiac involvement (detected on screening tests) improve outcome? What is a safe screening strategy, with acceptable risk for patients and preferably low costs? Is there a potential role for biomarkers in screening for myocardial involvement? In chapter 2, direct evidence is provided, by speckle tracking strain analyses, that subclinical LV systolic dysfunction contributes to impaired aerobic capacity in patients with SSc. This is not a surprising finding, but this correlation has not yet been established in SSc patients by conventional echocardiographic measures of systolic function such as ejection fraction or TDI. Another finding was the fact that LV systolic dysfunction as assessed by speckle tracking strain analysis was the only independent predictor of ventricular arrythmias (ventricular ectopics and non-sustained ventricular tachycardias). Thus, speckle tracking strain analysis may contribute in improvement of risk stratification among patients with SSc as arrhythmias are concerned. It is not yet clear however if the rhythm abnormalities as defined for the analysis contribute directly to morbidity or mortality. Considering its safety, low costs and easy accessibility, speckle tracking strain analysis may contribute as a screening tool for assessment of primary cardial involvement in SSc.

Body function measured by patient reported questionnaires

In rheumatology, health status measures on the level of body functions and structures and activities and participation, preferably complying with OMERACT Principles (5), are recommended for assessment, intervention management and outcome evaluation. Examples of such measures are the Health Assessment Questionnaire, Short Form-36 (6;7) and the (UCLA) Scleroderma Clinical Trial Consortium GI Tract Instrument (8). In this thesis two patient-reported questionnaires for the evaluation of body function were evaluated: the MHISS (mouth handicap in Systemic Sclerosis) and the MHQ (Michigan Hand questionnaire).

- The MHISS questionnaire, which was translated and adapted into the Dutch language, is a questionnaire addressing SSc specific mouth and face symptoms. It has been used in a number of publications (9;10).
- The MHQ was developed for general hand disorders and validated for other inflammatory conditions as Rheumatoid arthritis (11). In this thesis the MHQ demonstrated both adequate validity and responsiveness in patients with SSc. The MHQ contains questions addressing a broad spectrum of hand complaints; overall hand function, activities of daily living, pain, work performance, aesthetics, and patient satisfaction with hand function. In contrast, the Cochin Hand Function Scale (a frequently used and SSc validated patient reported questionnaire (12;13), contains 18 items focusing on functional tasks (kitchen, dressing, hygiene, office and other items include turning a doorknob, cutting with scissors, and turning a key in a lock).

Moreover, we used the FSFI (Female Sexual Function Index). No recommendation exists on measures how to address sexual complaints. However, since the publication of the study presented in Chapter 3, several studies addressed sexual function in SSc women using the FSFI as outcome measurement (14-18). It has thus been confirmed that the impact of SSc on sexual activity is considerable. Women with SSc were less likely to be sexually active and significantly more likely to be sexually impaired than women from a general population and had significantly worse lubrication and pain scores (15). Other correlates with sexual function in women with SSc are: body image dissatisfaction, longer disease duration and not being married (18), body esteem and depression (14).

As was explained in chapter 1, the ICF classification may be helpful in clarifying to what extent these questionnaires describe disease experience. Linking rules have been developed to relate each item of a health-status measure to the ICF category representing its content in a specific and precise manner (19) . One item, domain or questionnaire may refer to categories in multiple ICF domains such as a body structure, a body function, an activity or a contextual factor. For rheumatoid arthritis (RA), the content of two of the most widely used health status measures, the HAQ and AIMS2,

was compared with the comprehensive ICF Core Set (20). It was found that the HAQ is an instrument that exclusively covers the component activity and participation, whereas the AIMS2, which can be considered a generic health status measure specific to RA, also covers aspects of the component body functions, particularly emotional functions, sleep functions, pain and stiffness and more detailed activities. A similar analysis in osteoarthritis resulted in the recommendation for the comprehensive measurement of functioning to select a instrument with a low diversity ratio (for disease-specific aspects) as well as another instrument with a high diversity ratio (for broader aspects of functioning in other ICF domains) (21).
Although an ICF core set for SSc is currently being developed, the present lack of such a core set hampers a formal comparison of the relevance of the content of measures such as previously described questionnaires. For example, MHISS items could be linked to the ICF; “My lips are retracted and/or my cheeks are sunken“, referring to the domain body structures and “I have difficulties speaking clearly” referring to body function. Certainly, future studies on this subject would provide more knowledge on specific patient reported outcomes (range and level of precision). Moreover, a systematic evaluation of SSc outcomes can identify domains not covered by a specific instrument.

Part II: activities and participation; work ability

Work is an significant part of patient’s involvement in daily life and society and has been recognized as an important outcome of disease (22). A systematic review included in this thesis demonstrated considerable work disability in SSc. However, most included studies had a cross sectional design and used employment rates and permanent work disability as outcome measures while data on sick leave or presenteeism (productivity) were presented in a few. Moreover, there was no uniformity in the definitions of work disability that were employed. It was concluded that future studies are needed, preferably with a prospective and international design and clear definitions of all outcomes, including sick leave and presenteeism, taking differences in age, sex and other socio-demographic variables such as education into account.
In a recent study including 2327 patients from 18 European countries enrolled in the Digital Ulcer Outcome (DUO) Registry, patients reported more impairment in work and daily activities and required more support from others with increasing numbers of digital ulcers (23). For this study, an adapted functional assessment questionnaire was used based on the existing, validated Work Productivity and Activity Impairment Questionnaire (WPAI) (24) in which work impairment is determined based on employment status, work days or hours missed, normal working hours per week, and productivity impairment while working. The score included a patients score for their productivity impairment due to DU (range 0-10), impairment of daily activities other than work due to DU (range 0-10) and need for help quantified as days or hours of

paid and unpaid help needed. In future research, work ability should be included as outcome measure in trials evaluating pharmalogical or nonpharmalogical treatment. For this purpose, validated outcome measures for work ability are essential.

Part III: Contextual factors

Delay or incorrect diagnosis, lack of information or support at time of diagnosis and difficulties in access to treatment, rehabilitation and care are some of the problems that patients with a rare disease as systemic sclerosis may experience (25). The patients’ perspective is essential when evaluating health services in Systemic Sclerosis from a qualitive point of view. A survey included in this thesis exploring health care and information needs of SSc patients confirmed unmet health care needs in the physical and psychological domains, and unmet information needs on medical subjects. In a recent survey on online information needs, 185 / 469 (43%) SSc patients responded to a questionnaire evaluating current disease-related internet use**,** the perceived importance of diverse information topics, and their usefulness of 8 widely used online health services. 151/185 (82%) SSc patients had internet access, and used this to search for information on their disease (85%), treatment, medication, and lifestyle (58–63%), or visiting a peer support forum (39%).
In a recent cross sectional survey 94 % (237/251) of Dutch Rheumatoid Arthritis patients reported insufficient knowledge about the contents and accessibility of at least one health care service (including information on what health services offer and how to access them). However, 69% of the patients reported an information need about the content and 61% on the accessibility (26). An important finding was thus the fact that a perceived lack of knowledge did not automatically imply an information need, since fewer patients reported an information need than a knowledge deficit and correlations between knowledge and information need were weak.
Hardly any information can be found on SSc patients’ knowledge of their disease. In a survey including 1437 members of 12 provincial chapters of the Scleroderma Society of Canada, 54% indicated they had limited scleroderma, 18% diffuse disease, and 23% did not know what type of scleroderma they had. Adequate level of knowledge concerning their disease is a prerequisite for effective self-management (27), but forcing information to patients who are not open for it may diminish the chance of a successful behavioral change (28). Examples of relevant behavioral changes or self management are; timely consulting physicians in case of medical urgencies or issues, giving up smoking, usage of aids and devices, applying energy conservation techniques and home based exercise programs.

Another important improvement of health care in SSc lies within standard of care in diagnostics and treatment according to evidence based assessment (29-32). Screening

programs consisting of regular clinical assessment, pulmonary function testing, echocardiography, and lung radiology resulted in improved identification of SSc patients with cardiopulmonary involvement and better identification of patients with less advanced lung disease (33;34). Specific recommendations can also be found for gastro-intestinal disease (35) and PAH (34). Despite annually performed 'basic' diagnostic tools including echocardiograms and pulmonary function tests (PFT), significant practice variability in diagnosing PAH was demonstrated (36) between Canadian hospitals suggesting that SSc experience does play a role in diagnosing complications. Moreover, differences in approach to patient care in PAH between specialists was demonstrated, with rheumatologists being more involved with overall patient function and quality of life (more use of functional and quality of life tools) while the cardiologists/ pulmonologists were more comfortable with the specific quantification and effects of the pulmonary status perse (37). These findings strongly support a multidisciplinary approach with annual comprehensive screening in SSc specialized centres. In this disease evaluation, patient reported questionnaires covering the different ICF domains can contribute to the early identification of disease symptoms or other risk factors in functioning that may require specific treatment or guidance.

In the Leiden University Medical Center, a yearly recurrent, two day- diagnostic and care program for SSc patients has been implemented for patients referred by non-academic as well as academic rheumatologists. The program consists of: a) an inventory of the patients problems and needs by means of questionnaires; b) clinical history taking and clinical evaluation by a specialized rheumatologist, pulmonologist, cardiologist, and health professionals (occupational therapist, physical therapist and/or social worker) according to the patients needs; c) pulmonary function tests, High Resolution CT thorax, ECG, transthoracal echography of the heart, cardio-pulmonary exercise testing (CPET), 24h rhythm registration and blood analysis; Diagnostic outcome parameters are discussed in a multidisciplinary meeting and result into a treatment advice for the referring rheumatologist . In the first 3 months time, 44 patients were referred (38). Treatment advice resulted in further referral to another specialist (n=2 respectively cardiac electrophysiology and endocrinology), analysis of suggestive pulmonary arterial hypertension (n=3), change of supportive medical therapy (n=3) or immunosuppressive therapy (n=4). Health professional advice resulted into further intensive treatment by a peripheral physical therapist (n=9), referral to a psychotherapist (n=1). The required period between the program and reporting the advice to the referring rheumatologist was 3,5 weeks. The program has continued in the past years; so far 350 individual patients were evaluated.

Part IV: Non pharmacological care

Evidence for effectiveness of SSc-specific psychosocial and rehabilitation intervention programs is scarce and trials are hindered by relatively low numbers of potential participants. The Scleroderma Patient-centered Intervention Network (SPIN) is an international collaboration of patient organisations, clinicians and researchers aiming to develop a research infrastructure to test accessible, low-cost self-guided online interventions to reduce disability and improve HRQL for SSc patients (39). Interventions that are being developed concern (1) general SSc self-management, (2) support for better coping with emotional distress; (3) support for managing body image distress and (4) physical and occupational therapy for hands.

In the randomized trial "MIDAS" (Multidisciplinaire Intensieve DAgbehandeling Sclerodermie) rehabilitation consisted of a multiple components. Therefore, it is unclear which components contributed most to the treatment effect on general outcomes as Health Assesment Questionnaire. The choice for the rehabilitation strategy employed in this study is based on the previously established effectiveness of multidisciplinary treatment in other inflammatory disease (40) and was supported by the department's experience. In other rehabilitation studies, specific focus on hand function resulted in relatively more improvement of hand outcome measures (41). Moreover, improvement of some hand outcome measures was not sustained 12 weeks after completion of after our team care program, suggesting a decrease in exercise intensity at home. Evidence on the effectiveness of advised home exercises is scarce. Partly non-sustained results were seen in SSc patients 9 weeks after completion of a 9 week supervised program (42), whereas most improvement was demonstrated 2 and 4 months after a 2 week rehabilitation course including prescribed home exercises (43).

Limited evidence is present on self management in Systemic Sclerosis (44). A mail-delivered self-management program including a workbook (chapters containing learning activities, with action plans modeled after the arthritis self-management programs) and exercise DVD (demonstrated face, mouth, hand, arm, and leg exercise) resulted in improved hand function and self-efficacy, decreased depression, fatigue, and pain; with self-efficacy for pain demonstrating the only statistically significant change. The same authors subsequently developed an interactive internet-based version of the SSc self-management program (45); showing promising results. In rheumatoid arthritis patients an internet-mediated physical activity intervention was employed (46) with high satisfaction rates from patients. In SSc however, an important condition for participation in home based programs is relatively stable disease, sufficient patient's knowledge and accessible coaching if necessary. Further study in the direction of this kind of rehabilitation strategies is warranted including comparison between in-patient and out-patients modalities. Home based treatment of (hand) function supported by SSc specialized health care providers may allow financial savings in health recourses as well as minimizing intrusion into patients' everyday life.

Since benefits of physical exercise on general health have been established (47), exercise training may also contribute to well being in SSc patients. The safety of exercise training for SSc patients was an important finding of the MIDAS trial including aerobic exercise (1 hr twice a week). Safety was confirmed in a non controlled study by Pinto et al including eleven SSc patients completing a 12 week training program (1 hr twice a week) (48) and a controlled study by Oliviera et al describing the results of 7 SSc patients and healthy controls completing an 8 week training program (40 minutes twice a week).

Efficacy of exercise programs can be established by improved aerobic capacity as well as muscle strength and function. Aerobic capacity is defined as the maximum amount of oxygen the body can use during intense exercise and is a function both of cardio-respiratory performance and the maximum ability to remove and utilize oxygen from circulating blood. Aerobic capacity is expressed as maximum oxygen uptake (VO2max); cardiac output x 13.4 x hemoglobulin x (arterial oxygen saturation-venous oxygen saturation). The degree to which aerobic capacity can be improved by training varies widely largely due to genetics, “low responders” will see little or no benefit, “high responders” may double their capacity(49). The average response to training in healthy persons is estimated as a 17% increase in VO_2max. In the MIDAS trial, study patients achieved a mean improvement of the six minute walk distance (6MWD) of 42.8 meter, but no improvement of peak oxygen uptake was seen. Since disease consequences in SSc include both cardiorespiratory performance and microvascular system, a negative effect of the disease on trainability may be present. After a 8 week training program however, increased peak Oxygen uptake in both SSc patients and controls was demonstrated by Oliviera et al (50) thus illustrating that improving aerobic capacity is feasible in SSc patients. In this study patients with pulmonary involvement were excluded, which is unfortunate because lung involvement is a common complication in SSc. Sub analysis for patients with interstitial lung disease (ILD) in MIDAS was not possible due to the relatively small number of patients.

Recently, the American Thoracic Society and European Respiratory Society stated “Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors” (51). This review concerned various pulmonary illnesses, explicitly for ILD patients it was concluded that ‘evidence suggests that pulmonary rehabilitation may result in meaningful short-term benefits’. In 57 patients with Interstitial Lung Disease due to various causes, 6MWD improved with a mean of 35 m (95% CI 6 to 64 m) after completion of a 8 week exercise training program as compared with weekly telephone support, but oxygen uptake did not improve (52). Currently, a multicentre randomized controlled trial including 116 patients with ILD is conducted which hopefully will provide further information (53) on trainability. In 183 patients with various forms of pulmonary arterial hypertension a sustained improved 6MWD and peak oxygen consumption at 3 and 15 week after initiating a 3 week exercise training in a hospital with continued training at home (54). The results were impressive: the mean six-minute walk distance increased 96 meters in the exercise training group and decreased 15 meters in a control group, exceeding improvements described for all types of advanced therapy in PH. Adverse events, such as respiratory infection, syncope or pre-syncope, occurred in 13% of patients. The optimal exercise training program for PH remains currently unknown. Slow, incremental exercise protocols at low intensity and short duration are often used initially.

In conclusion, further studies on exercise training in SSc patients, especially those with organ involvement may provide more guidance in the risk-benefit determination in general. For individual patients however, tailored exercise prescription preceded by exercise assessment to diagnose cardiovascular co morbidities is warranted.

Non-pharmacological interventions for SSc patients require dedicated and preferably experienced SSc health professionals (HP). In the Netherlands, a few SSc specialized hospitals provide services and research projects from which patients living relatively nearby may benefit.

Currently a network is being developed in collaboration with the Dutch society for SSc patients ‘NVLE-connect’ for HP all over the Netherlands, providing a platform for exchanging experience and educational purpose. The NVLE-connect network was preceded by the EUSHnet, a project funded by EULAR, which was launched in 2012 in order to improve non-pharmacological care and reduce inequity through an international network of health professionals working in SSc. Both initiatives will hopefully contribute to a standard of non-pharmacological care for SSc patients.

Reference List

(1) Clements PJ, Lachenbruch PA, Furst DE, Paulus HE, Sterz MG. Cardiac score. A semiquantitative measure of cardiac involvement that improves prediction of prognosis in systemic sclerosis. Arthritis Rheum 1991; 34(11):1371-80.

(2) Khanna D, Gladue H, Channick R, Chung L, Distler O, Furst DE et al. Recommendations for screening and detection of connective-tissue disease associated pulmonary arterial hypertension. Arthritis Rheum 2013;10.

(3) Kahan A, Allanore Y. Primary myocardial involvement in systemic sclerosis. Rheumatology (Oxford) 2006; 45 Suppl 4:iv14-7.:iv14-iv17.

(4) Allanore Y, Meune C, Vonk MC, Airo P, Hachulla E, Caramaschi P et al. Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of patients with systemic sclerosis. Ann Rheum Dis 2010; 69(1):218-21.

(5) Furst DE. Outcome measures in rheumatologic clinical trials and systemic sclerosis. Rheumatology (Oxford) 2008; 47 Suppl 5:v29-30. doi: 10.1093/rheumatology/ken269.:v29-v30.

(6) Furst D, Khanna D, Matucci-Cerinic M, Clements P, Steen V, Pope J et al. Systemic sclerosis - continuing progress in developing clinical measures of response. J Rheumatol 2007; 34(5):1194-200.

(7) Steen VD, Medsger TA, Jr. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 1997; 40(11):1984-91.

(8) Khanna D, Hays RD, Maranian P, Seibold JR, Impens A, Mayes MD et al. Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. Arthritis Rheum 2009; 61(9):1257-63.

(9) Maddali-Bongi S, Landi G, Galluccio F, Del RA, Miniati I, Conforti ML et al. The rehabilitation of facial involvement in systemic sclerosis: efficacy of the combination of connective tissue massage, Kabat's technique and kinesitherapy: a randomized controlled trial. Rheumatol Int 2011; 31(7):895-901.

(10) Mouthon L, Rannou F, Berezne A, Pagnoux C, Guilpain P, Goldwasser F et al. Patient preference disability questionnaire in systemic sclerosis: a cross-sectional survey. Arthritis Rheum 2008; 59(7):968-73.

(11) van der Giesen FJ, Nelissen RG, Arendzen JH, de JZ, Wolterbeek R, Vliet Vlieland TP. Responsiveness of the Michigan Hand Outcomes Questionnaire--Dutch language version in patients with rheumatoid arthritis. Arch Phys Med Rehabil 2008; 89(6):1121-6.

(12) Duruoz MT, Poiraudeau S, Fermanian J, Menkes CJ, Amor B, Dougados M et al. Development and validation of a rheumatoid hand functional disability scale that assesses functional handicap. J Rheumatol 1996; 23(7):1167-72.

(13) Rannou F, Poiraudeau S, Berezne A, Baubet T, Le-Guern V, Cabane J et al. Assessing disability and quality of life in systemic sclerosis: construct validities of the Cochin Hand Function Scale, Health Assessment Questionnaire (HAQ), Systemic Sclerosis HAQ, and Medical Outcomes Study 36-Item Short Form Health Survey. Arthritis Rheum 2007; 57(1):94-102.

(14) Maddali BS, Del RA, Mikhaylova S, Baccini M, Matucci CM. Sexual Function in Italian Women with Systemic Sclerosis Is Affected by Disease-related and Psychological Concerns. J Rheumatol 2013; 40(10):1697-705.

(15) Levis B, Burri A, Hudson M, Baron M, Thombs BD. Sexual activity and impairment in women with systemic sclerosis compared to women from a general population sample. PLoS One 2012; 7(12):e52129.

(16) Levis B, Hudson M, Knafo R, Baron M, Nielson WR, Hill M et al. Rates and correlates of sexual activity and impairment among women with systemic sclerosis. Arthritis Care Res (Hoboken) 2012; 64(3):340-50.

(17) Impens AJ, Rothman J, Schiopu E, Cole JC, Dang J, Gendrano N et al. Sexual activity and functioning in female scleroderma patients. Clin Exp Rheumatol 2009; 27(3 Suppl 54):38-43.

(18) Knafo R, Haythornthwaite JA, Heinberg L, Wigley FM, Thombs BD. The association of body image dissatisfaction and pain with reduced sexual function in women with systemic sclerosis. Rheumatology (Oxford) 2011; 50(6):1125-30.

(19) Cieza A, Brockow T, Ewert T, Amman E, Kollerits B, Chatterji S et al. Linking health-status measurements to the international classification of functioning, disability and health. J Rehabil Med 2002; 34(5):205-10.

(20) Stucki G, Cieza A. The International Classification of Functioning, Disability and Health (ICF) Core Sets for rheumatoid arthritis: a way to specify functioning. Ann Rheum Dis 2004; 63 Suppl 2:ii40-ii45.:ii40-ii45.

(21) Stamm T, Geyh S, Cieza A, Machold K, Kollerits B, Kloppenburg M et al. Measuring functioning in patients with hand osteoarthritis--content comparison of questionnaires based on the International Classification of Functioning, Disability and Health (ICF). Rheumatology (Oxford) 2006; 45(12):1534-41.

(22) world health organisation. International Classification of Functioning, Disability and Health: ICF. 2001.

(23) Guillevin L, Hunsche E, Denton CP, Krieg T, Schwierin B, Rosenberg D et al. Functional impairment of systemic scleroderma patients with digital ulcerations: results from the DUO Registry. Clin Exp Rheumatol 2013; 31(2 Suppl 76):71-80.

(24) Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993; 4(5):353-65.

(25) Kole A, Faurisson F. Rare diseases social epidemiology: analysis of inequalities. Adv Exp Med Biol 2010; 686:223-50. doi: 10.1007/978-90-481-9485-8_14.:223-50.

(26) Meesters J, de B, I, van den Berg M, Fiocco M, Vliet VT. Unmet information needs about the delivery of rheumatology health care services: a survey among patients with rheumatoid arthritis. Patient Educ Couns 2011; 85(2):299-303.

(27) Taal E, Rasker JJ, Wiegman O. Patient education and self-management in the rheumatic diseases: a self-efficacy approach. Arthritis Care Res 1996; 9(3):229-38.

(28) van Weel-Baumgarten E. Patient-centred information and interventions: tools for lifestyle change? Consequences for medical education. Fam Pract 2008; 25 Suppl 1:i67-70.

(29) Kowal-Bielecka O, Landewe R, Avouac J, Chwiesko S, Miniati I, Czirjak L et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Ann Rheum Dis 2009; 68(5):620-8.

(30) Hudson M, Assayag D, Caron M, Fox BD, Hirsch A, Steele R et al. Comparison of different measures of diffusing capacity for carbon monoxide (DLCO) in systemic sclerosis. Clin Rheumatol 2013; 32(10):1467-74.

(31) Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009; 34(6):1219-63.

(32) Bombardieri S, Medsger TA, Jr., Silman AJ, Valentini G. The assessment of the patient with systemic sclerosis. Introduction. Clin Exp Rheumatol 2003; 21(3 Suppl 29):S2-S4.

(33) Nihtyanova SI, Tang EC, Coghlan JG, Wells AU, Black CM, Denton CP. Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study. QJM 2010; 103(2):109-15.

(34) Humbert M, Yaici A, de GP, Montani D, Sitbon O, Launay D et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. Arthritis Rheum 2011; 63(11):3522-30.

(35) Baron M, Bernier P, Cote LF, Delegge MH, Falovitch G, Friedman G et al. Screening and therapy for malnutrition and related gastro-intestinal disorders in systemic sclerosis: recommendations of a North American expert panel. Clin Exp Rheumatol 2010; 28(2 Suppl 58):S42-S46.
(36) Harding S, Khimdas S, Bonner A, Baron M, Pope J. Best practices in scleroderma: an analysis of practice variability in SSc centres within the Canadian Scleroderma Research Group (CSRG). Clin Exp Rheumatol 2012; 30(2 Suppl 71):S38-S43.
(37) Huscher D, Pittrow D, Distler O, Denton CP, Foeldvari I, Humbert M et al. Interactions between rheumatologists and cardio-/pulmonologists in the assessment and use of outcome measures in pulmonary arterial hypertension related to systemic sclerosis. Clin Exp Rheumatol 2010; 28(2 Suppl 58):S47-S52.
(38) Schuerwegh AJM, Schouffoer AA, Beaart-van de Voorde LJJ, Tromp FJM, Ninaber MK, Huizinga TWJ et al. Yearly, Standardized, Comprehensive Assessment and Treatment Advice for Patients with Systemic Sclerosis (SSc): Feasibility of a Day Care Program. Arthritis & Rheumatism 60[60 Suppl:S427-8.]. 2009.
(39) Kwakkenbos L, Jewett LR, Baron M, Bartlett SJ, Furst D, Gottesman K et al. The Scleroderma Patient-centered Intervention Network (SPIN) Cohort: protocol for a cohort multiple randomised controlled trial (cmRCT) design to support trials of psychosocial and rehabilitation interventions in a rare disease context. BMJ Open 2013; 3(8):e003563.
(40) Tijhuis GJ, Zwinderman AH, Hazes JM, Van Den Hout WB, Breedveld FC, Vliet Vlieland TP. A randomized comparison of care provided by a clinical nurse specialist, an inpatient team, and a day patient team in rheumatoid arthritis. Arthritis Rheum 2002; 47(5):525-31.
(41) Maddali BS, Del RA, Galluccio F, Tai G, Sigismondi F, Passalacqua M et al. Efficacy of a tailored rehabilitation program for systemic sclerosis. Clin Exp Rheumatol 2009; 27(3 Suppl 54):44-50.
(42) Bongi SM, Del RA, Galluccio F, Sigismondi F, Miniati I, Conforti ML et al. Efficacy of connective tissue massage and Mc Mennell joint manipulation in the rehabilitative treatment of the hands in systemic sclerosis. Clin Rheumatol 2009; 28(10):1167-73.
(43) Antonioli CM, Bua G, Frige A, Prandini K, Radici S, Scarsi M et al. An individualized rehabilitation program in patients with systemic sclerosis may improve quality of life and hand mobility. Clin Rheumatol 2009; 28(2):159-65.
(44) Poole JL, Skipper B, Mendelson C. Evaluation of a mail-delivered, print-format, self-management program for persons with systemic sclerosis. Clin Rheumatol 2013; 32(9):1393-8.
(45) Poole JL, Mendelson C, Skipper B, Khanna D. Taking charge of systemic sclerosis: a pilot study to assess the effectiveness of an internet self-management program. Arthritis Care Res (Hoboken) 2013;10.
(46) van den Berg MH, Ronday HK, Peeters AJ, Voogt-van der Harst EM, Munneke M, Breedveld FC et al. Engagement and satisfaction with an Internet-based physical activity intervention in patients with rheumatoid arthritis. Rheumatology (Oxford) 2007; 46(3):545-52.
(47) Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ 2006; 174(6):801-9.
(48) Pinto AL, Oliveira NC, Gualano B, Christmann RB, Painelli VS, Artioli GG et al. Efficacy and safety of concurrent training in systemic sclerosis. J Strength Cond Res 2011; 25(5):1423-8.
(49) Bouchard C, An P, Rice T, Skinner JS, Wilmore JH, Gagnon J et al. Familial aggregation of VO(2max) response to exercise training: results from the HERITAGE Family Study. J Appl Physiol (1985) 1999; 87(3):1003-8.
(50) Oliveira NC, dos Santos Sabbag LM, de Sa Pinto AL, Borges CL, Lima FR. Aerobic exercise is safe and effective in systemic sclerosis. Int J Sports Med 2009; 30(10):728-32.

(51) Spruit MA, Singh SJ, Garvey C, Zuwallack R, Nici L, Rochester C et al. An official american thoracic society/european respiratory society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013; 188(8):e13-e64.
(52) Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax 2008; 63(6):549-54.
(53) Dowman L, McDonald CF, Hill C, Lee A, Barker K, Boote C et al. The benefits of exercise training in interstitial lung disease: protocol for a multicentre randomised controlled trial. BMC Pulm Med 2013; 13:8. doi: 10.1186/1471-2466-13-8.:8-13.
(54) Grunig E, Lichtblau M, Ehlken N, Ghofrani HA, Reichenberger F, Staehler G et al. Safety and efficacy of exercise training in various forms of pulmonary hypertension. Eur Respir J 2012; 40(1):84-92.

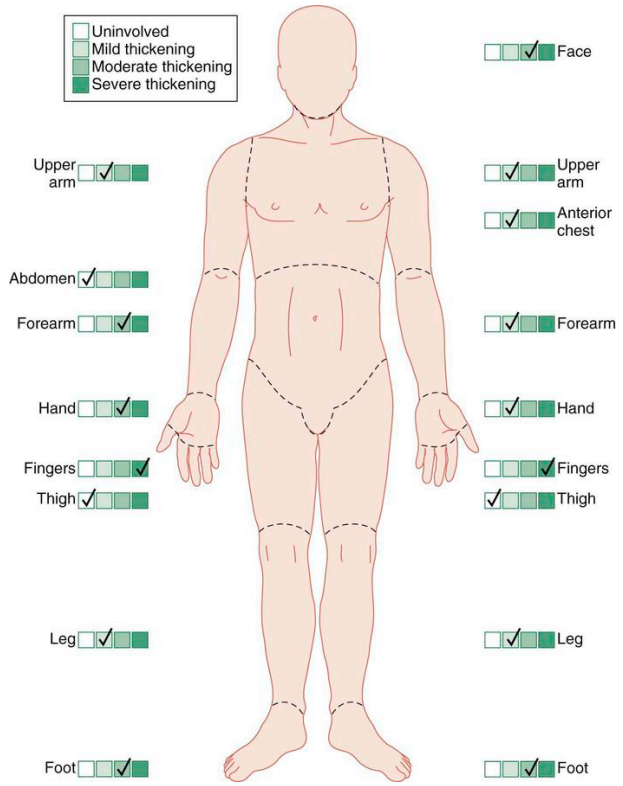
CHAPTER 10

Nederlandse samenvatting

Hoofdstuk 1

Systemische Sclerose (SSc) is een zeldzame aandoening van het bindweefsel met onbekende oorzaak en zeer variabele expressie. De ziekte wordt gekenmerkt door de trias inflammatie, vasculopathie en fibrosering (toename van bindweefsel) (1). De meest karakteristieke uiting van vasculopathie is het fenomeen van Raynaud: een aanvalsgewijze tri-, of di-fasische verkleuring van de vingertoppen van wit naar blauw en vervolgens rood. Fibrosering van de organen wordt gezien in o.a. de longen, het hart en het maagdarmstelsel. In de huid leidt de fibrose tot verstrakking (sclerodermie). De prevalentie van SSc in Nederland wordt geschat op 8.9 per 100.000 inwoners (2).

De variabiliteit in het ziektebeloop wordt bepaald door verschillen in huidbetrokkenheid en orgaan manifestaties. Op basis van klinische kenmerken kan SSc worden verdeeld in twee belangrijke subtypes. Dit zijn: a) gelimiteerde cutane SSc (LcSSc) waarbij de fibrosering van de huid zich beperkt tot de distale delen van de ledematen en er zich een matige en geleidelijke langzame fibrose van de inwendige organen kan voordoen



Figuur 1 voorbeeld van een modified Rodnan skin score

en b) diffuus cutane SSc (DcSSc) met snel voortschrijdende fibrosering van de huid van bovenarmen/benen en/of romp en een hoog risico op orgaancomplicaties in de eerste ziektejaren. Met een huidscore kan het onderscheid tussen beide vormen kan worden gemaakt en kan de uitgebreidheid van de huidverandering worden gedocumenteerd. De modified Rodnan skin score (mRSS) is de meest gebruikte score in klinisch onderzoek (3). Hierbij wordt het lichaam wordt verdeeld in 17 zones (zie figuur 1), waarin de huiddikte met een schaal van 0-3 wordt uitgedrukt.

Het fenomeen van Raynaud komt bij 3 tot 5 % van de algemene populatie voor zonder complicaties (4). Het kan echter ook de eerste manifestatie van SSc zijn. In een prospectieve studie ontwikkelde zich na een gemiddelde follow-up duur van 4 jaar bij 12.6% van de patiënten met een ‘primaire’ Raynaud een zekere Systemische Sclerose (5). Het onderscheid tussen een primaire Raynaud en SSc kan mede gemaakt worden met behulp van het nagelriem onderzoek en bepaling van antistoffen. Nagelriem microscopie is een techniek waarmee capillairen zichtbaar worden gemaakt; de combinatie van reuze capillairen, bloedingen en afname van capillair dichtheid zijn typische veranderingen die passen bij een SSc nagelriem patroon (6). SSc specifieke autoantistoffen (anti-Centromeer, anti-Scl-70, anti-RNA polymerase III) kunnen helpen om de diagnose te stellen, maar de afwezigheid ervan sluit SSc niet uit; tot 11% van de patiënten met SSc testen negatief op antinucleaire antilichamen. Autoantistoffen dragen bij aan het vaststellen van een prognose door de correlaties tussen SSc specifieke autoantistoffen en diverse orgaan complicaties (7).

Het voornaamste kenmerk van vroege ziekte is verstrakking ofwel verdikking van de huid (sclerodermie), of (in een vroege fase) zwelling van de handen; de zogenaamde ‘puffy’ handen/vingers (8). Daarbij kunnen de handen krachteloos zijn, door discrete tendinitis, artritis of myo/neuropathie. De krachteloosheid wordt in geval van een niet-onderkende SSc vaak geduid als een carpaal tunnel syndroom (CTS). Bij patiënten met actieve SSc kunnen fibrineuze afzettingen in peesschedes resulteren in een wrijvend geluid bij bewegen, de zogenaamde friction rubs. Myositis (indien aanwezig) heeft vaak een matige Creatine Kinase (CK) verhoging, maar is een prognostisch ongunstige factor (9). De inflammatie en later fibrose kan leiden tot microstomie en tendinogene of articulaire contracturen. Het sicca syndroom is vaak zeer hinderlijk aanwezig.

In 2013 zijn de ACR/Eular classificatie criteria voor Systemische Sclerose gepubliceerd (10). Volgens deze classificatie kan bij een score van ≥9 worden gesproken van een zekere SSc. Items die zijn opgenomen in deze classificatie zijn: huidverdikking van de vingers tot voorbij de Meta carpo phalangeale (MCP) gewrichten, puffy fingers of verdikte huid van alleen de vingers, littekens aan de vingertoppen door verminderde circulatie (pitting scars), zweertjes aan de vingers (digitale ulcera), teleangieectasieën, afwijkende nagelriem capillaroscopie, Raynaud fenomeen, pulmonale hypertensie en/of interstitiële longziekte en SSc-specifieke auto-antistoffen.

De mortaliteit van SSc is aanzienlijk: in een Canadese studie (11) werd bij 158 patiënten tussen 1994 en 2004 een 5-jaars overleving van 90%, en 10-jaars overleving van 82% gevonden. Overleden personen hadden vaker cardiale betrokkenheid, interstitiële longziekte, gastro-intestinale aandoeningen en renale crisis. In Eustar studie (EULAR Scleroderma Trials and Research group) was bij 234 personen die overleden aan de gevolgen van SSc In de (EUSTAR) database interstitiële fibrose de meest voorkomende oorzaak van overlijden (12). Bij patiënten met ernstige interstitiële fibrose bleek het grootste verlies in longfunctie op te treden in de eerste vier jaar na aanvang van ziekte, terwijl symptomen hierbij ontbraken (13). Daarbij lijken auto-antistoffen en niet zozeer de uitgebreidheid van de huidfibrose bij te dragen aan het identificeren van patiënten die het risico lopen een ernstige interstiële long fibrose te ontwikkelen (14). Risico stratificatie is van belang, zodat bij actieve ziekte door immuun modulatoire behandeling schade kan worden verminderd of verdere schade voorkomen (15). Bij patiënten met SSc worden met name 'niet specifieke interstitiële pneumonitis' (NSIP) en 'usual interstitiële pneumonitis' (UIP) gezien (16). De andere belangrijke long manifestatie is Pulmonale Arteriële Hypertensie (PAH): primair een ziekte gekenmerkt door pulmonale vasculaire weerstand veroorzaakt door proliferatie en contractie van de gladde spiercellen van de pulmonale arterioles. PAH komt in circa 10% van de patiënten met SSc voor.

Cardiale betrokkenheid bij SSc kan bestaan uit myocarditis en pericarditis, met name bij vroege en actieve ziekte, maar ook relaxatie- en pompfunctie stoornissen door fibrose en geleidingstoornis kunnen optreden (17). In een autopsie studie werd in het hart bij 70% van patiënten met SSc fibrose waargenomen, tegenover 37% in een controlegroep (18). Verandering in de micro-circulatie, verstoorde perfusie en ook ontstekingsactiviteit kunnen leiden tot fibrose met verminderde contractiliteit, met een risico op een geleidingstoornis tot gevolg (19). In de Eustar database (Europese database met 7073 SSc patiënten) werd in een cross-sectionele studie door middel van conventionele echocardiografie bij 5.4% een verminderde linker ventrikel (LV) ejectie fractie gevonden. Hogere leeftijd, mannelijk geslacht, aanwezigheid van digitale ulcera, myositis en longbetrokkenheid waren significant geassocieerd met cardiale problematiek (20). Het gebruik van calciumblockers was geassocieerd met minder LV dysfunctie, zodat een protectief effect gesuggereerd werd. De prognose van patiënten met cardiale betrokkenheid is somber als deze eenmaal klinisch manifest is (19), hetgeen de noodzaak voor het ontwikkelen valideren van meer sensitieve beeldvormende technieken duidelijk maakt.

Wat nierbetrokkenheid betreft is de scleroderma renale crise (SRC) de meest gevreesde complicatie. Patiënten met een ziekteduur van < 4 jaar, diffuse of snel progressieve huid betrokkenheid, anti-RNA polymerase III positiviteit en het gebruik van glucosteroïden > 15 mg/dag worden als belangrijke risicofactoren gezien (21;22). In het gastro-intestinale systeem kunnen functiestoornissen optreden als gevolg van spieratrofie en fibrose, mogelijk voorafgegaan door neuropathie. Dit kan leiden tot pijn, dysfagie, reflux, vroege verzadiging, opgeblazen gevoel, braken, diarree, constipatie, fecale incontinentie en malabsorptie en hierdoor substantieel gewichtsverlies (23). Fibrosering en vasculaire veranderingen kunnen ook urogenitale klachten veroorzaken (24;25).

De medische behandeling bestaat uit ondersteunende maatregelen enerzijds (behandeling infectieuze complicaties, therapie bij ulcera, verlichting gastro-intestinale complicaties, voeding supplementen bij malabsorptie), en behandeling gericht op ontsteking en fibrose anderzijds (26). Vroege herkenning van complicaties cruciaal, omdat de therapie dient te worden afgestemd op de individuele patiënt, afhankelijk van de omvang en ernst van orgaanbetrokkenheid en het stadium van de ziekte, actief of inactief. Niet medicamenteuze behandeling kan bestaan uit fysieke rehabilitatie, educatieve programma's, ondersteuning van zelfmanagement en psychologische ondersteuning. Hoewel er toenemende aandacht is voor niet-medicamenteuze behandeling, hebben beschikbare studies vaak een klein aantal deelnemende patiënten en soms een niet-gecontroleerde opzet (27).

Patiënten met SSc hebben te kampen met een onzeker ziektebeloop, wisselende impact op lichamelijk functioneren en beperkte behandel mogelijkheden. Bovendien worden ze vaak geconfronteerd met een veranderd uiterlijk; verandering van gelaatstrekken door huid verstrakking en verkleinde mondopening (microstomie), contracturen, teleangiectasiëen, pigment veranderingen en digitale ulcera. Er is toenemende aandacht voor de psychische belasting die dit met zich meebrengt. Een significant verminderde mentale kwaliteit van leven en milde tot matige depressie bij een aanzienlijk aantal patiënten met SSc werden aangetoond, evenals een laag zelfbeeld (28-30). Vanuit medisch oogpunt wordt de impact van een ziekte vaak uitgedrukt in een mate van fysieke beperking. De Internationale Classificatie van Functioneren (ICF) van de Wereldgezondheidsorganisatie (WHO) beschrijft het functioneren van mensen in bredere zin, inclusief de factoren die op het functioneren van invloed zijn (31). In dit schema staat de patiënt centraal en worden de volgende domeinen beschreven: a) ziektekenmerken (body functions en structures), b) activiteiten en maatschappelijke participatie, c) contextuele factoren als omgeving (o.a. klimaat, sociale status en beschikbare behandeling) en d) persoonlijke kenmerken van patiënt (bijvoorbeeld bewegingsangst).

Een selectie van ICF domeinen of categorieën die als minimale norm dienen voor de rapportage over gezondheid en functioneren van patiënten wordt een 'ICF core set' genoemd. Voor SSc is deze core set in ontwikkeling (32). Een core set kan helpen te verduidelijken in hoeverre gevalideerde meet instrumenten ziekte beleving van een patiënt beschrijven.

De doelstelling van dit proefschrift was het verkrijgen van meer inzicht in de impact van SSc op de gezondheid van patiënten, met betrekking tot de ICF hoofdstukken Body functies en structuren, Activiteiten en Participatie en Contextuele factoren, zoals revalidatie.

Hoofdstuk 2

Middels 'speckle tracking strain analysis' werd de linkerventrikelfunctie van 104 patiënten met SSc vergeleken met 37 gezonde controle personen, en werd de relatie met conventionele echocardiografie-parameters, inspanning capaciteit en 24 uur ritme registratie geëvalueerd. Er was geen significant verschil in ventrikel volumes of linker ventrikel ejectie fractie (LVEF) tussen de patiënten met SSc en controle personen. Er werd echter wel een significant verschil gezien in de geschatte pulmonale arteriële systolische druk (PASP), diastolische functie parameters en longitudinale en circumferentiële strain, allen ten nadele van de patiënten met SSc. Bovendien werd bij multivariate analyse een onafhankelijke correlatie gezien van de afzonderlijke strain waardes en inspanningcapaciteit. Tenslotte werd bij de patiënten met een afwijkende ritmeregistratie een vertraagde globale, longitudinale en circumferentiële strain gevonden. Er werd geconcludeerd dat speckle tracking strain analysis een geschikte techniek is voor het vast stellen van subklinische linkerventrikeldysfunctie.

Hoofdstuk 3

Tot voor kort was er meer bekend over de negatieve invloed van SSc op de seksuele functie bij mannen dan bij vrouwen. Deze cross-sectionele studie vergeleek de seksuele functie en zorgen over seksualiteit (seksuele distress) van 37 vrouwen met SSc met die van gezonde controle personen. Ook werd de correlatie van seksuele functie met ziekte karakteristieken bij vrouwen met SSc geëvalueerd. Hiervoor werden gevalideerde vragenlijsten als de Female Sexual Function Index (FSFI) en de Female Sexual Distress Scale (FSDS) gebruikt. Bij 70% van de patiënten werd verminderde seksuele functie gezien, bij 57% verhoogde seksuele distress. Seksuele dysfunctie, gedefinieerd als zowel verminderde seksuele functie als verhoogde seksuele distress, was aanwezig bij 47% van de patiënten. Bij patiënten met een verminderde seksuele functie werd meer relationele onvrede en langere duur van de ziekte waargenomen. Het gebruik van antidepressiva, meer depressieve symptomen, en een langere duur van de ziekte waren statistisch significant geassocieerd met meer seksuele distress. Multivariate analyses toonden aan dat relationele onvrede de enige variabele was die significant geassocieerd was met een lage seksuele functie bij patiënten met SSc. Depressie was de enige variabele die significant geassocieerd was met seksuele distress. Hetzelfde patroon van associaties werd gevonden in de gezonde controlegroep.

Hoofdstuk 4

De Franse generieke vragenlijst 'Mouth handicap in Systemic Sclerosis (MHISS) evalueert 'mond handicap' bij patiënten met SSc; de beperkingen in mondfunctie, droogheid van de slijmvliezen en esthetische bezwaren door een veranderd uiterlijk. De MHISS werd vertaald, getest door 16 SSc patiënten en aangepast waar nodig. Vervolgens werden diverse aspecten van validiteit getoetst in een groep van 52 patiënten met SSc. De divergente validiteit toetst of het instrument in staat is om onderscheid te maken tussen 'bekende groepen' met de verwachte verschillen in scores. Convergente validiteit bepaalt hoe sterk is het instrument gecorreleerd met andere meet instrumenten. Interne consistentie beschouwt de samenhang van de verschillende vragen binnen de vragenlijst, en de test-hertest betrouwbaarheid toetst de reproduceerbaarheid.
Binnen de groep van 52 deelnemende patiënten bleken bij degenen met hoge MHISS scores significant meer algemene beperkingen (Health Assessment Questionnaire (HAQ), meer beperking van de maximale mondopening (MMO), meer subjectieve xerostomie (droge mond) en meer objectieve xerostomie (droge ogen). Spearman correlaties met dezelfde parameters waren matig, de interne consistentie was voldoende, evenals de test - hertest betrouwbaarheid. Geconcludeerd werd dat de Nederlandse versie van de MHISS goede psychometrische eigenschappen toonde en nuttig is bij de beoordeling van de mondhandicap bij SSc patiënten.

Hoofdstuk 5

In hoofdstuk 5 werden de validiteit en responsiviteit van de Michigan Hand Questionnaire (MHQ) bij patiënten met SSc beoordeeld. De MHQ bevat 57 items en 6 domeinen: functie, activiteiten van het dagelijks leven, pijn, werk, esthetiek en tevredenheid. Hieruit kunnen 6 subschalen en een totaal score worden uitgerekend. De data werden verzameld bij de studie beschreven in hoofdstuk 8.
Drieënvijftig patiënten (28 in de interventiegroep en 25 in de controlegroep) voltooiden de MHQ bij aanvang en na 12 weken. De overige uitkomstmaten waren: de HAQ (Health Assessment Questionnaire), Hand Mobiliteit in Sclerodermie (HAMIS), Sequential Occupational Dexterity Assessment (SODA), grijpkracht, pinch grip en modified Rodnan Huid Score (mRSS). De validiteit werd bepaald door het berekenen van Spearman correlatiecoëfficiënten tussen de baseline MHQ totale score, subschalen en andere uitkomstmaten. De responsiviteit werd alleen in de interventiegroep geëvalueerd aan de hand de Standardized Response Mean (SRM), Effect Size (ES), en Responsiviteit Ratio (RR). Een 'treatment effect' (verschil tussen de interventie en controlegroep) werd berekend door middel van een pooled ES.
Significante correlaties werden gezien tussen de totaalscore van de MHQ en de HAQ (r = -0.62), HAMIS (r = -0.54), SODA (r = 0.47), SODA Pain (r = 0.32) en MRSS (r = 0.46).

De ES van de MHQ totale score in de interventiegroep was 0.49, het geen beter was dan die van alle andere uitkomstmaten. Soortgelijke resultaten werden verkregen voor de SRM en RR. De gepoolde ES van het verschil tussen interventie-en controlegroep voor de MHQ totale score was 0.86. Geconcludeerd werd dat de MHQ voldoende validiteit en responsiviteit toonde bij patiënten met een SSc, en daarmee een geschikt instrument lijkt om in deze patiënten groep de handfunctie te evalueren.

Hoofdstuk 6

Door middel van een systematische review van de literatuur werd de arbeidsparticipatie en factoren van invloed bij SSc patiënten beschreven. Twaalf klinische studies met kwantitatieve informatie over de arbeidssituatie van SSc patiënten en/ of factoren die samenhangen met arbeid ongeschiktheid (work disability, WD) werden geselecteerd. De methodologische kwaliteit werd beoordeeld aan de hand van drie aspecten (selection bias, information bias en statistical bias) en bleek laag in 11 van de 12 studies. Arbeidsparticipatie varieerde tussen 11% en 82% na een gemiddelde ziekteduur van 2.5 tot 14 jaar. Er was matig bewijs voor een verband tussen meer functionele beperkingen, meer ziekte specifieke symptomen en slechtere kwaliteit van leven aan de ene kant en de aanwezigheid van WD anderzijds. Er was matig bewijs voor de afwezigheid van een associatie tussen WD en leeftijd, geslacht en SSc subtype. Inconsistent bewijs werd gezien voor een verband tussen WD en opleiding of ziekteduur. Geconcludeerd werd dat WD een belangrijke uitkomst is bij patiënten met SSc, die geassocieerd is met functionele beperkingen, ziektespecifieke symptomen en slechtere kwaliteit van leven. Dit benadrukt de noodzaak van onderzoek naar interventies ter voorkoming of vermindering van WD bij patiënten met SSc, vooral bij patiënten met een slechtere gezondheidstoestand.

Hoofdstuk 7

Deze cross-sectionele studie inventariseerde de zorg- en informatiebehoefte en tevredenheid over geboden zorg bij 77 patiënten met SSc. Hiertoe werd een vragenlijst gebruikt met 27 vragen die verdeeld werden in diverse domeinen: zorg voor lichamelijke klachten, psychische klachten, steun systeem, arbeid en dagelijkse activiteiten, overige gezondheidvragen en informatie behoefte. Ook werd naar de voorkeur van de patiënt met betrekking tot de wijze en organisatie van zorgverlening en informatieverstrekking gevraagd. Van 83% van de respondenten gaf 42 % aan één of meer onvervulde zorgvragen te hebben, waarbij de hoogste percentages van patiënten met onvervulde zorgvragen werden gezien in de fysieke (30%) en psychologische (20%) domeinen. De hoogste percentages van patiënten met informatie behoeften werden gevonden voor medische onderwerpen (20-28%). Meer onvervulde zorgbehoefte was geassocieerd

met slechter psychisch functioneren, en een hogere informatiebehoefte met slechter fysiek functioneren en een diagnose diffuse SSc. Een jaarlijks, gestandaardiseerd, multidisciplinair diagnostisch programma werd als een geprefereerd als zorgmodel (59%) en de reumatoloog als een favoriete bron van informatievoorziening (75%).

Hoofdstuk 8

Een gerandomiseerde gecontroleerde studie evalueerde de veiligheid en effectiviteit van een multidisciplinair zorgprogramma voor patiënten met SSc, door deze te vergelijken met gebruikelijke poliklinische zorg. Dit zorgprogramma had als werktitel Multidisciplinaire Intensieve DAgbehandeling Sclerodermie (MIDAS). Het vond plaats op de Reumatologie Ambulante Zorg afdeling van het Leids Universitair Medisch Centrum, destijds ‘Sole Mio Ambulant’, met een frequentie van één dag per week en een totale duur van 12 weken. De dagbehandeling bestond verschillende onderdelen: A) groepsessies met oefeningen ter verbetering van de conditie, hand/mond oefeningen en educatie; B) individuele behandelingen door de reumatoloog, ergotherapeut, fysiotherapeut, maatschappelijk werker en reumatologie verpleegkundige, afhankelijk van de individuele behoeften van de patiënten; en C) individuele oefeningen bij een fysiotherapeut in de buurt (1 maal/week) en een home-based oefenprogramma (tenminste 6 dagen per week). Uitkomstmaten waren: de Hand Mobiliteit in Sclerodermie (HAMIS) test, handgrijpkracht, maximale mondopening (MMO), 6-minuten loopafstand (6MWD), de maximale aërobe capaciteit (VO2max), Checklist Individual Strength 20 (CIS - 20), SSc Health Assessment Questionnaire (HAQ), en Short Form 36 (SF-36). Metingen vonden plaats op baseline en 12 en 24 weken.
Achtentwintig patiënten werden door randomisatie toegewezen aan de interventie groep, 25 aan de controlegroep. Vijfentwintig patiënten (89%) in de interventiegroep voltooiden het programma. Na 12 weken was er een significante grotere verbetering van knijpkracht (2.2 versus -1.8, P < 0,001), MMO (1.4 versus -0.9 mm, p = 0.01), 6MWD (42.8 versus 3.9, P = 0.02), en HAQ score (-0.18 versus 0.13, P = 0.02) in de interventiegroep ten opzichte van de controlegroep. De verschillen voor de andere uitkomstmaten toonden geen statistisch significant verschil. Na 24 weken bleef alleen het effect op de MMO aanwezig. Geconcludeerd kon worden dat in SSc patiënten een 12-weken durend multidisciplinaire dagbehandeling effectiever was dan de reguliere ambulante zorg met betrekking tot diverse functionele uitkomstmaten.

Reference List

(1) Medsger TA, Jr. 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(2):255-73, vi.

(2) Vonk MC, Broers B, Heijdra YF, Ton E, Snijder R, van Dijk AP et al. Systemic sclerosis and its pulmonary complications in The Netherlands: an epidemiological study. Ann Rheum Dis 2009; 68(6):961-5.

(3) Clements PJ, Lachenbruch PA, Seibold JR, Zee B, Steen VD, Brennan P et al. Skin thickness score in systemic sclerosis: an assessment of interobserver variability in 3 independent studies. J Rheumatol 1993; 20(11):1892-6.

(4) LeRoy EC, Medsger TA, Jr. Raynaud's phenomenon: a proposal for classification. Clin Exp Rheumatol 1992; 10(5):485-8.

(5) Koenig M, Joyal F, Fritzler MJ, Roussin A, Abrahamowicz M, Boire G et al. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. Arthritis Rheum 2008; 58(12):3902-12.

(6) Cutolo M, Sulli A, Pizzorni C, Accardo S. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. J Rheumatol 2000; 27(1):155-60.

(7) Nihtyanova SI, Denton CP. Autoantibodies as predictive tools in systemic sclerosis. Nat Rev Rheumatol 2010; 6(2):112-6.

(8) Clements PJ, Furst DE. Cutaneous involvement in Systemic Sclerosis. Systemic Sclerosis. 2 ed. 2004. 129-49.

(9) Jung M, Bonner A, Hudson M, Baron M, Pope J, On Behalf Of The Canadian Scleroderma Research Group Csrg. Myopathy is a poor prognostic feature in systemic sclerosis: results from the Canadian Scleroderma Research Group (CSRG) cohort. Scand J Rheumatol 2014.

(10) van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A et al. 2013 Classification Criteria for Systemic Sclerosis: An American College of Rheumatology/ European League Against Rheumatism Collaborative Initiative. Arthritis Rheum 2013;NA.

(11) Al-Dhaher FF, Pope JE, Ouimet JM. Determinants of morbidity and mortality of systemic sclerosis in Canada. Semin Arthritis Rheum 2010; 39(4):269-77.

(12) Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010; 69(10):1809-15.

(13) Steen VD, Conte C, Owens GR, Medsger TA, Jr. Severe restrictive lung disease in systemic sclerosis. Arthritis Rheum 1994; 37(9):1283-9.

(14) Steen V. Predictors of end stage lung disease in systemic sclerosis. Ann Rheum Dis 2003; 62(2):97-9.

(15) Walker UA, Tyndall A, Czirjak L, Denton C, Farge-Bancel D, Kowal-Bielecka O et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 2007; 66(6):754-63.

(16) Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med 2002; 165(12):1581-6.

(17) Kahan A, Coghlan G, McLaughlin V. Cardiac complications of systemic sclerosis. Rheumatology (Oxford) 2009; 48 Suppl 3:iii45-8. doi: 10.1093/rheumatology/kep110.:iii45-iii48.

(18) Follansbee WP, Miller TR, Curtiss EI, Orie JE, Bernstein RL, Kiernan JM et al. A controlled clinicopathologic study of myocardial fibrosis in systemic sclerosis (scleroderma). J Rheumatol 1990; 17(5):656-62.

(19) Kahan A, Allanore Y. Primary myocardial involvement in systemic sclerosis. Rheumatology (Oxford) 2006; 45 Suppl 4:iv14-7.:iv14-iv17.

(20) Allanore Y, Meune C, Vonk MC, Airo P, Hachulla E, Caramaschi P et al. Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of patients with systemic sclerosis. Ann Rheum Dis 2010; 69(1):218-21.

(21) Guillevin L, Berezne A, Seror R, Teixeira L, Pourrat J, Mahr A et al. Scleroderma renal crisis: a retrospective multicentre study on 91 patients and 427 controls. Rheumatology (Oxford) 2012; 51(3):460-7.

(22) Steen VD, Medsger TA, Jr. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis Rheum 1998; 41(9):1613-9.

(23) Ebert EC. Gastric and enteric involvement in progressive systemic sclerosis. J Clin Gastroenterol 2008; 42(1):5-12.

(24) Bhadauria S, Moser DK, Clements PJ, Singh RR, Lachenbruch PA, Pitkin RM et al. Genital tract abnormalities and female sexual function impairment in systemic sclerosis. Am J Obstet Gynecol 1995; 172(2 Pt 1):580-7.

(25) Ostojic P, Damjanov N. The impact of depression, microvasculopathy, and fibrosis on development of erectile dysfunction in men with systemic sclerosis. Clin Rheumatol 2007; 26(10):1671-4.

(26) Kowal-Bielecka O, Landewe R, Avouac J, Chwiesko S, Miniati I, Czirjak L et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Ann Rheum Dis 2009; 68(5):620-8.

(27) Poole JL. Musculoskeletal rehabilitation in the person with scleroderma. Curr Opin Rheumatol 2010; 22(2):205-12.

(28) Hudson M, Thombs BD, Steele R, Panopalis P, Newton E, Baron M. Health-related quality of life in systemic sclerosis: a systematic review. Arthritis Rheum 2009; 61(8):1112-20.

(29) Thombs BD, Taillefer SS, Hudson M, Baron M. Depression in patients with systemic sclerosis: a systematic review of the evidence. Arthritis Rheum 2007; 57(6):1089-97.

(30) van Lankveld WG, Vonk MC, Teunissen H, van den Hoogen FH. 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 (Oxford) 2007; 46(5):872-6.

(31) world health organisation. International Classification of Functioning, Disability and Health: ICF. 2001.

(32) Saketkoo LA, Escorpizo R, Keen KJ, Fligelstone K, Distler O. International Classification of Functioning, Disability and Health Core Set construction in systemic sclerosis and other rheumatic diseases: a EUSTAR initiative. Rheumatology (Oxford) 2012; 51(12):2170-6.

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Curriculum Vitae

Anne Schouffoer werd geboren op 15 Mei 1968 in Rotterdam. In 1988 behaalde zij het diploma van het Voortgezet Wetenschappelijk Onderzoek aan de RAS (Rotterdamse Dag en Avondscholengemeenschap) in Rotterdam, waarna zij een jaar in Cambridge als au-pair werkte. In 1989 begon zij aan de studie Geneeskunde in Leiden, in 1997 werd met succes het artsexamen afgerond. Hierna volgde een aanstelling als Assistent Geneeskunde Niet In Opleiding (AGNIO) op de afdelingen Interne Geneeskunde van het Rijnland ziekenhuis in Leiderdorp en de reumatologie afdeling “Sole Mio” van het LUMC in Leiden. Ook werkte zij tussentijds bij de ArbodienstWest, vestigingen Leiden en Rijswijk.

Haar opleiding tot internist tot startte in 1999 in het Groene Hart Ziekenhuis in Gouda (opleider Dr K.Heering), en werd van 2001 tot 2006 vervolgd in het LUMC (opleider prof. dr. A.E. Meinders). In het laatste jaar van de opleiding Interne Geneeskunde begon zij met de opleiding tot Reumatoloog (opleider prof. dr. F.C. Breedveld, opgevolgd door prof. dr. T.W.J. Huizinga). In de laatste fase van de opleiding begon zij aan het onderzoek waarvan de resultaten worden beschreven in dit proefschrift (onder leiding van prof. dr. T.P.M. Vliet Vlieland). Vanaf 01.09.2007 is zij ingeschreven in het register als reumatoloog. Van 2007 tot 2012 was zij werkzaam als reumatoloog in het Groene Hart Ziekenhuis in Gouda, en van 2012 tot heden in het Haga Ziekenhuis in Den Haag. Tevens hield zij vanaf 2007 een aanstelling bij de Reumatologie van het LUMC.

Op 21 Mei 2011 ontving zij van de patiënten vereniging voor mensen met sclerodermie (NVLE) de ‘NVLE award’ voor de studies uit dit proefschrift, wegens de bijdrage aan verbetering van zorg voor mensen met Systemische Sclerose.

Anne Schouffoer is samenwonend met Floor Meij en vier kinderen: Leander, Ciske, Fenna en Cas.

Publications

Embolization of a ruptured aneurysm in classic polyarteritis nodosa presenting as perirenal hematoma.
Schouffoer AA, Siegert CE, Arend SM, Thompson J, van Oostaijen JA. Arch Intern Med. 1998 Jul 13;158(13):

Impaired sexual function in women with systemic sclerosis: a cross-sectional study.
Schouffoer AA, van der Marel J, Ter Kuile MM, Weijenborg PT, Voskuyl A, Vliet Vlieland CW, van Laar JM, Vliet Vlieland TP. Arthritis Rheum. 2009 Nov 15;61(11):1601-8.

Needs and preferences regarding health care delivery as perceived by patients with systemic sclerosis.
Schouffoer AA, Zirkzee EJ, Henquet SM, Caljouw MA, Steup-Beekman GM, van Laar JM, Vlieland TP. Clin Rheumatol. 2011 Jun;30(6):815-24.

Randomized comparison of a multidisciplinary team care program with usual care in patients with systemic sclerosis.
Schouffoer AA, Ninaber MK, Beaart-van de Voorde LJ, van der Giesen FJ, de Jong Z, Stolk J, Voskuyl AE, Scherptong RW, van Laar JM, Schuerwegh AJ, Huizinga TW, Vlieland TP. Arthritis Care Res (Hoboken). 2011 Jun;63(6):909-17

Health care usage in Dutch systemic lupus erythematosus patients.
Zirkzee EJ, Steup-Beekman GM, **Schouffoer** AA, Henquet SM, Caljouw MA, Huizinga TW, Vlieland TP. Lupus. 2011 Oct;20(11):1147-54

Increased incidence of pregnancy complications in women who later develop scleroderma: a case control study.
van Wyk L, van der Marel J, Schuerwegh AJ, **Schouffoer** AA, Voskuyl AE, Huizinga TW, Bianchi DW, Scherjon SA. Arthritis Res Ther. 2011;13(6):R183.

Left ventricular dysfunction assessed by speckle-tracking strain analysis in patients with systemic sclerosis: relationship to functional capacity and ventricular arrhythmias.
Yiu KH, **Schouffoer** AA, Marsan NA, Ninaber MK, Stolk J, Vlieland TV, Scherptong RW, Delgado V, Holman ER, Tse HF, Huizinga TW, Bax JJ, Schuerwegh AJ. Arthritis Rheum. 2011 Dec;63(12):3969-78

Work status and its determinants among patients with systemic sclerosis: a systematic review.
Schouffoer AA, Schoones JW, Terwee CB, Vliet Vlieland TP. Rheumatology (Oxford). 2012 Jul;51(7):1304-14.

Heath-care utilization in Dutch systemic sclerosis patients.
Meijs J, Zirkzee EJ, **Schouffoer** AA, Henquet SM, Caljouw MA, Stijnen T, Huizinga TW, Schuerwegh AJ, Vliet Vlieland TP. Clin Rheumatol. 2013 Aug 28. [Epub ahead of print]

Translation, cross-cultural adaptation, and validation of the Mouth Handicap in Systemic Sclerosis questionnaire (MHISS) into the Dutch language.
Schouffoer AA, Strijbos E, Schuerwegh AJ, Mouthon L, Vliet Vlieland TP. Clin Rheumatol. 2013 Nov;32(11):1649-55

Translation, cross-cultural adaptation, and validation of the UCLA SCTC GIT 2.0 into the Dutch.
Meijs J, Pors D, Vliet Vlieland TPM, Huizinga TWJ, **Schouffoer AA.** Accepted Clinical and Experimental Rheumatology

Detection of pulmonary vasculopathy by novel analysis of oxygen uptake in patients with systemic sclerosis: association with pulmonary arterial pressures
Ninaber M, Hamersma W, **Schouffoer A**, Kovacs G, Olschewski H, Holman E, Ajmone Marsan N, Stolk J. Accepted Clinical and Experimental Rheumatology

In a standardized health care program the modified Rodnan Skin Score, HRCT-thorax and creatine phosphokinase contribute most to the start of immunosuppressive treatment in The Leiden Systemic Sclerosis Cohort
Meijs M, de Vries-Bouwstra JK, Ajmone Marsan N, Stijnen T, Ninaber MK, Huizinga TWJ, **Schouffoer AA**. Submitted Arthritis Care Research

Impact of pulmonary fibrosis and elevated pulmonary pressures on right ventricular function in patients with systemic sclerosis
Yiu KH, Ninaber MK, Kroft LJ, **Schouffoer AA**, Stolk J, Scherer HU, Meijs J, Tse HF, Delgado V, Bax JJ, Huizinga TWJ, Ajmone Marsan N. In preparation for submission to Eur J of Respiratory

Effectiveness of non-pharmacological interventions in systemic sclerosis: a systematic review
Willems LM, Vriezekolk JE, **Schouffoer AA**, Poole JL, PhD; Stamm TA; Boström C, Kwakkenbos L, Vliet Vlieland TPM, van den Ende CHM. In preparation for submission to the Annals of Rheumatic diseases

Lung structure and function relation in systemic sclerosis: application of lung densitometry in a prospective study
Ninaber MK, Stolk J, Smit J, Le Roy EJ, Kroft LJM, Bakker ME, de Vries Bouwstra JK**, Schouffoer AA,** Staring M, Stoel BC. Submitted