RHEUMATOLOGY

Rheumatology 2018;57:441–450
doi:10.1093/rheumatology/kex182
Advance Access publication 11 May 2017

Original article

Functional disability and its predictors in systemic sclerosis: a study from the DeSScipher project within the EUSTAR group

Veronika K. Jaeger[1], Oliver Distler[2], Britta Maurer[2], Laszlo Czirják[3], Veronika Lóránd[3], Gabriele Valentini[4], Serena Vettori[4], Francesco Del Galdo[5], Giuseppina Abignano[5], Christopher Denton[6], Svetlana Nihtyanova[6], Yannick Allanore[7], Jerome Avouac[7], Gabriele Riemekasten[8], Elise Siegert[9], Dörte Huscher[10], Marco Matucci-Cerinic[11], Serena Guiducci[11], Marc Frerix[12], Ingo H. Tarner[12], Beata Garay Toth[13], Beat Fankhauser[14], Jörg Umbricht[14], Anastasia Zakharova[15], Carina Mihai[16], Franco Cozzi[17], Sule Yavuz[18], Nicolas Hunzelmann[19], Simona Rednic[20], Alessandra Vacca[21], Tim Schmeiser[22], Valeria Riccieri[23], Paloma García de la Peña Lefebvre[24], Armando Gabrielli[25], Brigitte Krummel-Lorenz[26], Duska Martinovic[27], Codrina Ancuta[28], Vanessa Smith[29], Ulf Müller-Ladner[12] and Ulrich A. Walker[1]

Abstract

Objectives. The multisystem manifestations of SSc can greatly impact patients' quality of life. The aim of this study was to identify factors associated with disability in SSc.

Methods. SSc patients from the prospective DeSScipher cohort who had completed the scleroderma health assessment questionnaire (SHAQ), a disability score that combines the health assessment questionnaire and five visual analogue scales, were included in this analysis. The effect of factors possibly associated with disability was analysed with multiple linear regressions.

Results. The mean SHAQ and HAQ scores of the 944 patients included were 0.87 (S.D. = 0.66) and 0.92 (S.D. = 0.78); 59% of the patients were in the mild to moderate difficulty SHAQ category ($0 \leqslant \text{SHAQ} < 1$), 34% in the moderate to severe disability category ($1 \leqslant \text{SHAQ} < 2$) and 7% in the severe to very severe

[1]Department of Rheumatology, University Hospital Basel, Basel, [2]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [3]Department of Rheumatology and Immunology, Medical Center, University of Pécs, Pécs, Hungary, [4]Department of Rheumatology, Second University of Naples, Naples, Italy, [5]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, [6]Department of Rheumatology, University College London, Royal Free Hospital, London, UK, [7]Department of Rheumatology, University of Paris Descartes, Paris, France, [8]Department of Rheumatology, University Clinic Schleswig-Holstein, Lübeck, [9]Department of Rheumatology and Clinical Immunology, University Hospital Charité, [10]German Rheumatism Research Centre, Berlin, Germany, [11]Department of Rheumatology, University of Florence, Florence, Italy, [12]Department of Rheumatology and Clinical Immunology, Justus-Liebig University Giessen, Kerckhoff Clinic Bad Nauheim, Bad Nauheim, Germany, [13]Federation of European Scleroderma Associations Aisbl, Budapest, Hungary, [14]new-win SW Solutions AG, Suhr, Switzerland, [15]VA Nasonova Institute of Rheumatology, Moscow, Russian Federation, [16]Department of Internal Medicine and Rheumatology, Dr Ion Cantacuzino Clinical Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [17]Rheumatology Unit, Department of Medicine, University of Padova, Padova, Italy, [18]Department of Rheumatology, University of Marmara, Altunizade-Istanbul, Turkey, [19]Department of Dermatology, University of Cologne, Cologne, Germany, [20]Clinica Reumatologie, University of Medicine & Pharmacy, Cluj-Napoca, Romania, [21]II Chair of Rheumatology, University of Cagliari-Policlinico Universitario, Monserrato, Italy, [22]Department of Rheumatology and Immunology, Krankenhaus St Josef, Wuppertal, Germany, [23]Divisione di Reumatologia, Università di Roma La Sapienza, Roma, Italy, [24]Servicio de Reumatología, Hospital Universitario Madrid Norte Sanchinarro, Madrid, Spain, [25]Istituto di Clinica Medica Generale, Ematologia ed Immunologia Clinica, Università Politecnica delle Marche, Ancona, Italy, [26]Endokrinologikum Frankfurt, Frankfurt, Germany, [27]Division of Rheumatology, University Hospital of Split, Split, Croatia, [28]Rheumatology 2 Department, Clinical Rehabilitation Hospital, University of Medicine and Pharmacy 'Grigore T. Popa', Iasi, Romania and [29]Faculty of Internal Medicine, Ghent University, Ghent, Belgium

Submitted 27 September 2016; revised version accepted 29 March 2017

Correspondence to: Ulrich A. Walker, Department of Rheumatology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland. E-mail: ulrich.walker@usb.ch

CLINICAL SCIENCE

disability category ($2 \leqslant$ SHAQ $\leqslant 3$). The means of the visual analogue scales scores were in order of magnitude: overall disease severity (37 mm), RP (31 mm), pulmonary symptoms (24 mm), gastrointestinal symptoms (20 mm) and digital ulcers (19 mm). In multiple regression, the main factors associated with high SHAQ scores were the presence of dyspnoea [modified New York Heart Association (NYHA) class IV (regression coefficient B = 0.62), modified NYHA class III (B = 0.53) and modified NYHA class II (B = 0.21; all *vs* modified NYHA class I)], FM (B = 0.37), muscle weakness (B = 0.27), digital ulcers (B = 0.20) and gastrointestinal symptoms (oesophageal symptoms, B = 0.16; stomach symptoms, B = 0.15; intestinal symptoms, B = 0.15).

Conclusion. SSc patients perceive dyspnoea, pain, digital ulcers, muscle weakness and gastrointestinal symptoms as the main factors driving their level of disability, unlike physicians who emphasize objective measures of disability.

Key words: systemic sclerosis, functional disability, scleroderma health assessment questionnaire, predictors of disability

Rheumatology key messages

- Patients and physicians emphasize different aspects in the evaluation of SSc severity.
- Patients perceive dyspnoea, pain, digital ulcers, weakness and gastrointestinal symptoms as main factors of disability in SSc.
- Future research is needed to decipher, address and overcome the barriers to quality of life improvement in SSc.

Introduction

SSc is a rare, clinically heterogeneous multisystem disorder which greatly affects the patients' physical and psychological functioning and impairs their ability to participate in work and social activities. Substantial morbidity results from digital ulcers (DUs), skeletal muscle weakness, contractures, cardiopulmonary and gastrointestinal involvement [1–3]. One of the most formidable goals of care is to alleviate symptoms and disability and to improve the health-related quality of life (QoL) and functional ability [4].

Whereas physicians tend to emphasize objective measures of disease status, patients may perceive other aspects of their disease as more disabling or burdensome [5]. The evaluation of SSc severity and its impact on activities of daily living requires several measures due to multiple organ involvement; single organ outcome measures only provide limited information [6].

The HAQ is one of the most commonly used measures of disability in musculoskeletal disorders and is also used in SSc as a simple, inexpensive and practical way to reflect the patients' perspective [7–10]. It is a self-reported questionnaire consisting of 20 questions split across eight domains, addressing rising, eating, walking, hygiene, dressing, reach, grip and usual activities [11]. The HAQ was extended to form the scleroderma HAQ (SHAQ), a more disease-specific disability scale that incorporates the HAQ and five scleroderma-related visual analogue scales (VASs) into one score [6]. The five VASs in the SHAQ assess the level of impairment due the complications frequently observed in SSc outside the musculoskeletal system, namely RP, DUs, gastrointestinal symptoms, respiratory symptoms, as well as the overall severity of the disease from the patients' perspective [6]. The SHAQ is a reliable and valid measure of functional disability in SSc [6–8, 12, 13].

Several studies have assessed the impact of selected SSc-specific symptoms on patients' life [3, 14–17], or assessed overall QoL or functional disability and factors associated with it [1, 13, 18]. However, due to the rarity of the disease, most of these studies have a limited sample size and focus on sub-populations, for example only patients with DUs or patients with pulmonary hypertension [18–21]. Recently, one large internet-based survey assessed patients' perception of factors impacting on their daily lives, as well as health-related QoL [22]. This study, however, was a purely patient-based survey with no linkage to clinical data.

Our aim was therefore to prospectively analyse functional disability in a large cohort of SSc patients not selected for a particular organ manifestation, and to identify clinical factors contributing to impairment.

Methods

Study population and design

The DeSScipher (to decipher the optimal management of SSc [23, 24]) project is a multinational, longitudinal study embedded in the European Scleroderma Trials and Research (EUSTAR) group database [25, 26]. The DeSScipher project consisted of five observational trials (OTs) focusing on DU, hand arthritis, interstitial lung disease, pulmonary hypertension and severe heart disease. However, DeSScipher patients as such were not selected for any specific organ manifestations as the DeSScipher cohort consisted of EUSTAR patients being followed at DeSScipher centres during the DeSScipher project regardless of organ manifestations and eligibility into any

of the DeSScipher OTs (see the DeSScipher website for more detail [24]).

DeSScipher data were collected prospectively in a multicentre approach. Data collection for the DeSScipher project started in March 2013; however, the recording of the SHAQ within the DeSScipher database only started in October 2014, and was independent of particular organ manifestations, SSc treatments or eligibility for a specific DeSScipher OT. Data for this study were exported in August 2016. Each DeSScipher centre obtained ethical approval from its local ethics committee; written informed consent according to the Declaration of Helsinki was required from each patient prior to enrolment.

All patients had to fulfill either the 1980 ACR criteria for SSc or the 2013 ACR/EULAR criteria and were eligible for this analysis if they were above 18 years of age and had at least one SHAQ available [6, 27, 28]. Patients were classified as dc or lcSSc depending on the most severe skin involvement at the time of the study visit or any prior visit.

The HAQ built into the SHAQ has a recall period of 7 days, ranges from 0 to 3 and can be categorized into mild to moderate difficulty (score of 0 to <1), moderate to severe disability (score of 1 to <2) and severe to very severe disability (score of 2–3) [10, 11]. The VAS scales in the SHAQ assess the interference of the disease with daily activities and range from 0 (not limiting activities) to 100 (very severe limitation). In the original version of the SHAQ no combined score was built; instead the HAQ and the five VASs were assessed separately [6]. Georges *et al.* [29] proposed to average the eight HAQ categories and the five VASs (each downscaled to range from 0 to 3) into a composite SHAQ score ranging from 0 to 3. For this cross-sectional study, the first SHAQ recorded was analysed.

Statistical analysis

Depending on the categorical or continuous nature of the variables, frequencies and percentages or means (S.D.) were calculated. For categorical variables, between group comparisons were carried out using chi-squared tests or Fisher's exact tests; *t*-tests were used for continuous variables. Missing data of covariates were imputed using multiple imputations by chained equations [30, 31].

After defining possible predictors of functional disability *a priori* (Table 1), predictors were identified using univariable and multivariable linear regression analyses. We decided not to include the SSc subset of the patients and sclerodactyly in the multivariable model, as these variables are strongly related to the modified Rodnan skin score.

To compare levels of disability in patients with diffuse SSc and limited SSc we reduced the original model to factors that were strong and clinically significant predictors of functional disability in the overall patient group or were defined *a priori*.

The minimal clinical important difference (MCID) of the HAQ is stated to be ⩾0.22 [32]. As the SHAQ is based on the HAQ and has the same range, we applied this threshold also to the SHAQ. We treated a difference of ⩾10 mm as the MCID for the VAS components [32–34]. All analyses were performed with Stata/IC 13.1 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

At the time of the data export, 944 (38%) of the 2488 adult DeSScipher patients had a SHAQ score. During the time of the SHAQ collection, 2084 patients had a visit after the introduction of the SHAQ, and therefore 45% of eligible patients had a SHAQ score available; the demographic and disease characteristics of this study population are listed in Table 2. Of the 944 patients, 115 (12.2%) fulfilled only the 2013 ACR/EULAR criteria but not the 1980 ACR classification criteria for SSc. Patients included in the study were of similar age and sex distribution as the patients excluded for the lack of a SHAQ. Additionally, both groups had comparable disease durations and SSc subset distributions (data not shown).

Functional disability

The mean (S.D.) SHAQ score was 0.87 (0.66); 59.5% of the patients were in the lowest SHAQ category (score of 0 to <1), 34.0% had a score of 1 to <2 and 6.5% were in the category regarded as severe to very severe disability (score of 2–3). Patients fulfilling only the 2013 ACR/EULAR criteria but not the 1980 ACR criteria had a lower average SHAQ score [0.55 (S.D. 0.56)] than patients fulfilling the 1980 ACR classification criteria [0.91 (S.D. 0.66); $P < 0.001$]. Patients with dcSSc had a higher mean SHAQ score [0.96 (S.D. 0.65)], than patients with lcSSc [0.83 (S.D. 0.67); $P = 0.005$]. Of patients with dcSSc, 46.8% had mild to severe disability (scores 1–3) compared with 37.6% with lcSSc ($P = 0.003$).

The mean (S.D.) HAQ score was 0.92 (0.78); 53.8% of patients fell into the mild to moderate difficulty category (score <1), 34.1% into the moderate to severe disability (score ⩾1 to <2) and 12.1% into the severe to very severe disability (score ⩾2) category. Patients with diffuse SSc had a higher mean HAQ score than patients with lcSSc [1.04 (S.D. 0.77) *vs* 0.87 (S.D. 0.77); $P = 0.002$].

Of the five VASs included in the SHAQ, the highest values were reported on the overall disease severity VAS [mean = 37 (S.D. 27)]. Patients with dcSSc reported a higher level of limitation due to overall disease severity [mean = 40 mm (S.D. 27)] than patients with limited SSc [mean = 35 mm (S.D. 27); $P = 0.02$].

With respect to RP, the mean VAS impairment reported was 31 mm (S.D. 28). Patients with dcSSc reported a higher level of impairment due to RP [mean = 34 mm (S.D. 29)] than patients with lcSSc [mean = 29 mm (S.D. 27); $P = 0.01$].

The average perceived limitation due to pulmonary problems was 24 mm (S.D. 27). Patients with dcSSc reported a similar level of impairment due to pulmonary symptoms [mean = 24 mm (S.D. 27)] as patients with lcSSc (mean = 24 mm (S.D. 28); $P = 0.81$]. Patients in

Table 1 Description of possible predictors selected *a priori* for the analysis

Demographics
Age (years)
Sex (female/male)
Disease characteristics
Time since Raynaud's phenomenon onset (years)
Time since first non-Raynaud's phenomenon manifestation (years)
Modified Rodnan skin score (range 0–51)
Oesophageal symptoms (yes/no; dysphagia, reflux according to patient)
Stomach symptoms (yes/no; early satiety, vomiting according to patient)
Intestinal symptoms (yes/no; diarrhoea, bloating, constipation according to patient)
Any gastrointestinal symptoms (yes/no; any of oesophageal, stomach or intestinal symptoms)
Number of gastrointestinal symptoms (range 0–3; oesophageal, stomach and/or intestinal symptoms)
Dyspnoea (modified New York Heart Association functional class I to IV):
Class I: No limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea (shortness of breath)
Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in dyspnoea
Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes dyspnoea
Class IV: Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest.
Puffy fingers (yes/no; current scleroderma)
Digital ulcers (yes/no; current ulcers distal to or at the proximal IP joint)
Telangiectasia (yes/no)
Joint synovitis (yes/no; by rheumatologist's judgement)
Joint contractures (yes/no; by rheumatologist's judgement)
Muscle weakness (yes/no; by rheumatologist's judgement defined as a paresis unexplained by a neuropathy or contracture)
Muscle atrophy (yes/no; by rheumatologist's judgement)
FM (yes/no; by rheumatologist's judgement)
Systolic pulmonary artery pressure (mmHg; as estimated by echocardiography)
Single breath diffusing capacity for carbon monoxide (% of predicted)
Forced vital capacity (% of predicted)
Lung fibrosis on high resolution CT (yes/no)
Conduction blocks (yes/no; Atrioventricular-block, bundle branch blocks)
Diastolic dysfunction (yes/no)
Pericardial effusion (yes/no)
Left ventricular ejection fraction (%)
Laboratory
ACA (yes/no)
Anti-topoisomerase autoantibodies (Scl-70) positivity (yes/no)
Anti-RNA polymerase-III autoantibodies positivity (yes/no)
ESR (mm/h)
Serum creatinine kinase elevation (yes/no)

higher modified NYHA functional classes (as a proxy for dyspnoea, see Table 1) perceived a more marked pulmonary limitation than patients in modified NYHA class I [modified NYHA class IV, mean = 74 mm (S.D. 24); modified NYHA class III, mean = 61 mm (S.D. 24); modified NYHA class II, mean = 29 mm (S.D. 26); modified NYHA class I, mean = 11 mm (S.D. 19); $P < 0.001$].

With respect to gastrointestinal problems, patients reported a VAS mean of 20 mm (S.D. 26). There was no difference in the perceived impairment due to gastrointestinal problems between patients with dcSSc [mean = 18 mm (S.D. 25)] and lcSSc [mean = 21 mm (S.D. 27); $P = 0.11$]. Patients with a higher number of simultaneous gastrointestinal symptoms reported higher average VAS scores than patients with a low number of gastrointestinal symptoms [42 mm (S.D. 31) for patients reporting all of oesophageal, gastric and intestinal symptoms; 26 mm (S.D. 26) for patients reporting symptoms in two gastrointestinal regions; 16 mm (S.D. 23) for patients reporting symptoms in only one gastrointestinal region; *vs* 7 mm (S.D. 14) for patients reporting no gastrointestinal symptom; $P < 0.001$].

The VAS assessing the impairment due to the presence of DU had relatively low scores [mean = 19 mm (S.D. 28)]. Patients with dcSSc [mean = 22 mm (S.D. 30)] reported a higher level of impairment than patients with lcSSc [mean = 18 mm (S.D. 27); $P = 0.02$]. However, patients who had DU prior to enrolment, but not at the time of SHAQ reporting, had a mean DU VAS of 21 mm (S.D. 28), and patients suffering from DUs at the time of SHAQ completion reported a mean VAS of 53 mm (S.D. 33) ($P < 0.001$).

Predictors to functional disability

We first assessed the association of variables with the SHAQ with univariable analysis. The strongest predictor of disability was dyspnoea. In patients with modified

TABLE 2 Demographic and disease characteristics of the study population at the time of scleroderma HAQ assessment (n = 944)

Characteristics of the study population (n = 944)	
Age, mean (S.D.), years	56.8 (13.0)
Male sex, %	15.0
Disease characteristics	
Time since RP onset, mean (S.D.), years	14.8 (11.9)
Time since first non-RP manifestation, mean (S.D.), years	11.5 (9.1)
mRSS, mean (S.D.)	6.7 (7.1)
Cutaneous involvement, %	
Sine	6.9
Limited	56.5
Diffuse	36.6
Oesophageal symptoms, %	62.7
Stomach symptoms, %	26.6
Intestinal symptoms, %	38.1
Dyspnoea (modified NYHA functional class), %	
I	44.0
II	47.4
III	7.4
IV	1.2
Sclerodactyly, %	72.5
Puffy fingers, %	42.8
Digital ulcers, %	13.2
Telangiectasia, %	74.9
Joint synovitis, %	11.4
Joint contractures, %	50.5
Tendon friction rubs, %	4.6
Muscle weakness, %	16.7
Muscle atrophy, %	6.7
FM, %	4.0
Conduction blocks, %	17.7
Diastolic dysfunction, %	45.2
Pericardial effusion, %	1.8
LVEF, mean (S.D.), %	62.2 (5.4)
LVEF <50%, %	1.3
PAPsys, mean (S.D.), mmHg	29.8 (12.1)
PAPsys >40 mmHg, %	10.6
DLCO, mean (S.D.), % of predicted	63.3 (19.3)
FVC, mean (S.D.), % of predicted	94.8 (21.5)
FVC <80% of predicted, %	23.3
Lung fibrosis on HRCT, %	59.8
Laboratory parameters	
ANA positive, %	98.2
ACA positive, %	38.7
Scl-70 positive, %	48.4
RNAP-III positive, %	6.2
ESR, mean (S.D.), mm/h	19.8 (16.0)
Creatinine kinase elevation, %	6.4

DLCO: single breath diffusing capacity for carbon monoxide; FVC: forced vital capacity; HRCT: high resolution CT; LVEF: left ventricular ejection fraction; mRSS: modified Rodnan skin score; NYHA: New York Heart Association; PAPsys: systolic pulmonary artery pressure as estimated by echocardiography; RNAP-III: anti-RNA polymerase-III autoantibodies; Scl-70: anti-topoisomerase autoantibodies.

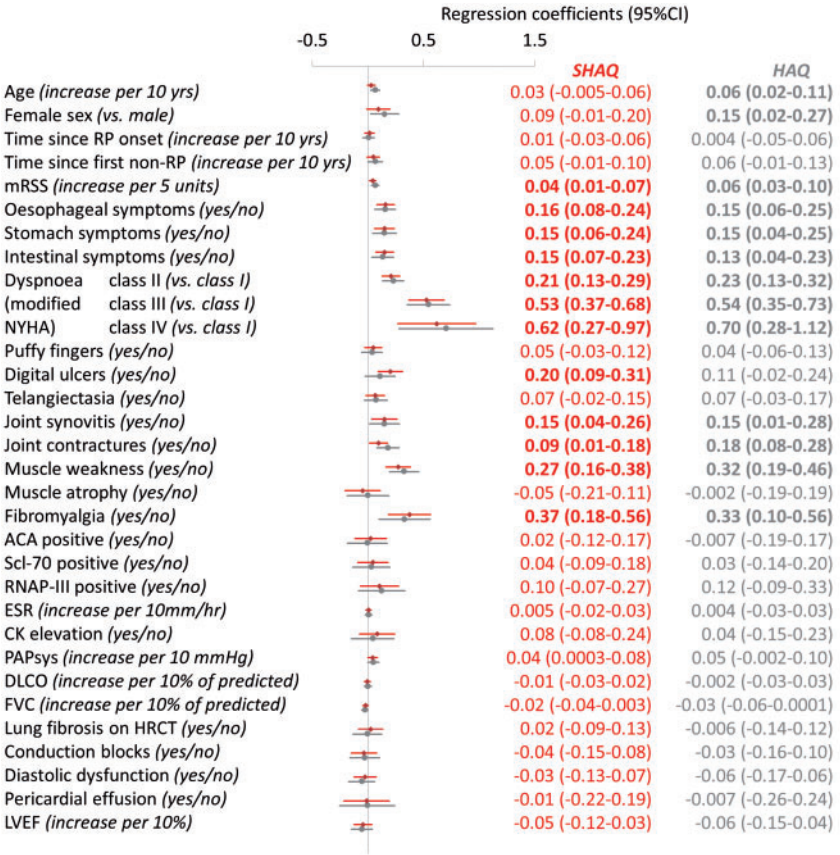
NYHA class IV the SHAQ score was on average 1.17 U (95% CI: 0.80, 1.53) higher than in patients with modified NYHA class I [modified NYHA class III: 0.88 U (95% CI: 0.73, 1.04); and modified NYHA class II: 0.40 U (95% CI: 0.32, 0.48) all *vs* modified NYHA class I]. Weaker, although still clinically important predictors were (in order of magnitude) muscle weakness [increase of 0.51 U (95% CI: 0.40, 0.62)], the presence of FM [increase of 0.47 U (95% CI: 0.25, 0.69)] and the three variables referring to gastrointestinal involvement [gastric 0.41 U (95% CI: 0.32, 0.50), oesophageal 0.38 U (95% CI: 0.29, 0.46) and intestinal symptoms 0.34 U (95% CI: 0.25, 9.42)].

The multivariable analysis of the SHAQ was in line with the results observed in univariable analysis. Dyspnoea remained the strongest predictor of functional disability. The SHAQ scores reported by patients with modified NYHA class IV, III or II were on average 0.62, 0.53 and 0.21 U higher than that of patients with modified NYHA class I (Fig. 1). In addition, both the presence of FM and muscle weakness were associated with higher levels of disability. Patients with FM reported on average a SHAQ value 0.37 U higher than that of patients without FM, and patients experiencing muscle weakness recorded on average a 0.27 U higher SHAQ (Fig. 1). Other factors contributing to disability included the presence of DUs, oesophageal, gastric and/or intestinal symptoms, joint contractures, and a more severe skin involvement (Fig. 1). Only dyspnoea, FM and muscle weakness remained clinically significant contributors to functional disability when applying the 0.22 threshold for the MCID [32].

None of the objective clinical measures were associated with a higher SHAQ score (Fig. 1). The changes in the average SHAQ scores were (in order of absolute magnitude): 10% higher left ventricular ejection fraction (−0.05 U), 10 mmHg higher systolic pulmonary artery pressure as estimated by echocardiography (0.04 U), presence of conduction blocks (−0.04 U), presence of a diastolic dysfunction (−0.03 U), 10% of predicted lower forced vital capacity (−0.02 U), 10% of predicted lower single breath diffusing capacity for carbon monoxide (−0.01 U) and the presence of pericardial effusion (−0.01 U).

Patients experiencing any gastrointestinal involvement (presence of oesophageal, gastric or intestinal symptoms) reported a clinically significant higher SHAQ [0.24 U (95% CI: 0.15, 0.32)] than patients reporting no gastrointestinal involvement. In multivariable analysis, patients with multiple simultaneous gastrointestinal symptoms also had higher SHAQ scores than those featuring symptoms in only one or two regions of the gastrointestinal tract (oesophagus, stomach or intestine). Patients reporting oesophageal, gastric and intestinal symptoms simultaneously had, on average, a SHAQ score of 0.46 U (95% CI: 0.34, 0.58) higher than patients reporting no gastrointestinal symptoms. Similarly, patients with symptoms in two or one gastrointestinal region also reported a higher functional disability than patients with no gastrointestinal problems [0.28 U (95% CI: 0.18, 0.38) and 0.13 U (95% CI: 0.04, 0.22), respectively].

Fig. 1 Predictors for the composite scleroderma HAQ and the HAQ scores in SSc patients

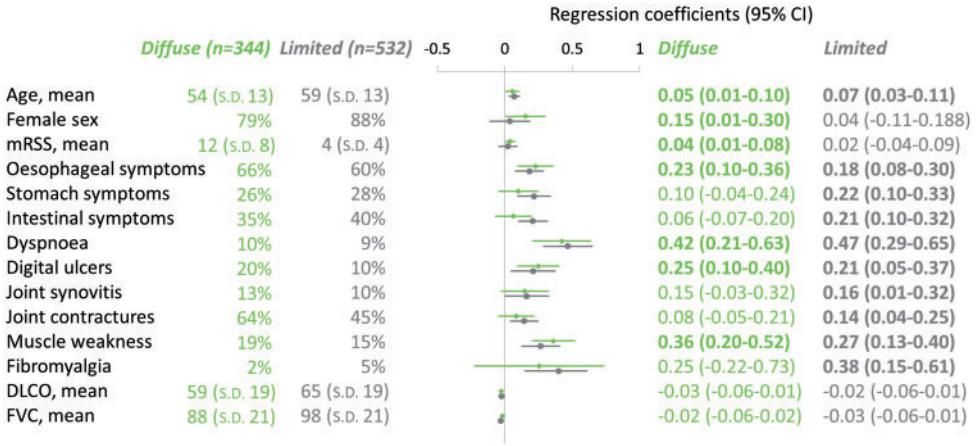


Multivariable regression coefficients with 95% CI for the composite SHAQ and the HAQ scores (both ranging from 0 to 3). Regression coefficients and their 95% CI are presented in bold if the 95% CIs do not include zero. DLCO: single breath diffusing capacity for monoxide; FVC, forced vital capacity; LVEF: left ventricular ejection fraction; mRSS; modified Rodnan skin score; NYHA: New York Heart Association; PAPsys systolic; pulmonary artery pressure as estimated by echocardiography; Scl-70: anti-topoisomerase autoantibodies; yrs: years.

The analysis of the HAQ scores showed impairment similar to the SHAQ. In univariable analysis in patients in modified NYHA functional class IV, the HAQ was on average 1.32 U (95% CI: 0.88, 1.75) higher than in patients in modified NYHA class I; respective values for patients in modified NYHA class III were 0.96 U (95% CI: 0.78, 1.14) and in patients in modified NYHA class II 0.46 U (95% CI: 0.37, 0.56), all *vs* modified NYHA I. Other factors associated with higher HAQ scores were (in order of magnitude): the presence of muscle weakness [0.59 U (95% CI: 0.46, 0.72)], the presence of muscle atrophy [0.50 U (95% CI: 0.30, 0.70)], the presence of FM [0.42 U (95% CI: 0.16, 0.67)], joint contractures [0.44 U (95% CI: 0.35, 0.54)], gastrointestinal symptoms [oesophageal −0.40 U (95% CI: 0.30, 0.50); gastric −0.43 U (95% CI: 0.32, 0.54); intestinal −0.3 U5 (95% CI: 0.25, 0.45)] and tendon friction rubs [0.40 U (95% CI: 0.16, 0.64)].

In multivariable analyses, patients with modified NYHA functional class IV had an average HAQ score of 0.70 U higher than patients with modified NYHA functional class I (modified NYHA class III: 0.54 U; modified NYHA class II: 0.23 U; all *vs* modified NYHA class I). The presence of FM (increase of 0.33 U) and of muscle weakness (increase of 0.32 U) were also strong and clinically important predictors of elevated HAQ scores (Fig. 1). The presence of any gastrointestinal problems, that is, the presence of oesophageal, stomach or intestinal symptoms, led to a clinically important average increase of 0.22 HAQ U (95% CI: 0.11, 0.31). Similarly, the number of simultaneous gastrointestinal symptoms was a strong predictor of an elevated HAQ; for patients reporting each of oesophageal, gastric and intestinal symptoms, the average HAQ increase was 0.44 U (95% CI: 0.30, 0.58), for patients reporting symptoms in two gastrointestinal regions the average increase was 0.26 U (95% CI: 0.14, 0.38) and for patients reporting symptoms in only one gastrointestinal region the HAQ increase was 0.11 U (95% CI: 0.002, 0.22) compared with patients reporting no gastrointestinal symptom.

Fig. 2 Predictors for the composite scleroderma HAQ in patients with diffuse and patients with lcSSc



Demographic and disease characteristic as well as multivariable regression coefficients with 95% CI for the composite SHAQ score (range 0 to 3) for patients with diffuse and limited cutaneous SSc. Regression coefficients and their 95% CI are presented in bold if the 95% CIs do not include zero. Age, increase per 10 years; DLCO and FVC, increase per 10% of predicted; dyspnoea, modified NYHA functional class III/IV *vs* modified NYHA functional class I/II; mRSS, increase per 5 points; all others, yes/no. DLCO: single breath diffusing capacity for monoxide; FVC: forced vital capacity; mRSS: modified Rodnan skin score; NYHA: New York Heart Association.

Disability in the SSc subsets

In patients with diffuse SSc (n = 344), the factors contributing to a clinically meaningful SHAQ increase were similar to those contributing in patients with lcSSc (n = 532; Fig. 2), namely dyspnoea (modified NYHA III/IV *vs* modified NYHA I/II increase of 0.42 U), muscle weakness (increase of 0.36 U) and gastrointestinal symptoms (Fig. 2). Patients with fibromyalgia also had on average a 0.25 U higher SHAQ (Fig. 2).

In both SSc subsets, the presence of multiple simultaneous gastrointestinal symptoms also strongly predicted disability. In patients with diffuse SSc, the SHAQ was on average 0.39 U (95% CI: 0.19, 0.59) higher in patients simultaneously reporting oesophageal, gastric and intestinal symptoms than in patients not reporting gastrointestinal symptoms. In the group of patients with lcSSc, this difference was even greater [0.60 U (95% CI: 0.44, 0.78)].

Discussion

Our study is by far the largest linking patients' self-assessed disability with objective clinical data and is also the first of its size to analyse a comprehensive set of clinical factors contributing to disability in an SSc population not selected for a particular organ manifestation or subset. The physicians' main attention while caring for SSc patients is often focused on objective measures of function, for example pulmonary function tests. These measures may, however, not reflect the patient's experience with the disease, self-perceived impact on QoL and functional capacity.

The most important factors predicting functional disability in our study were dyspnoea, gastrointestinal symptoms, FM, muscle weakness and the presence of DU, in line with the results of smaller studies [5, 15, 16, 20, 21, 35, 36]. Thus, there is a major difference between the factors driving patient perceived levels of disability and those emphasized by physicians (i.e. lung function testing, pulmonary arterial pressure estimates, etc.). In clinical practice, though, objective quantifications of gastrointestinal symptoms, FM, muscle weakness and DUs are rarely performed. Comparing the four specific VASs, the highest patient-rated limitation of daily life was due to RP, followed by pulmonary and gastrointestinal symptoms. A similar finding was observed in two surveys in which SSc patients ranked RP, gastrointestinal complications, musculoskeletal involvements and pain among the symptoms influencing their daily life the most [22, 37]. In contrast to our study, Strickland *et al.* [18] only found an association between functional disability and gastrointestinal involvement, but not with any other demographic or clinical variable. Similarly, Chow *et al.* [19] did not detect a correlation between NYHA functional class, the strongest predicting factor in our study, and functional disability in SSc patients with pulmonary arterial hypertension. One likely reason for this discrepancy is the limited sample size of 68 and 41 patients, respectively. Additionally, in the study by Chow *et al.* [19] the selection of patients might be another likely reason as the investigators only included SSc patients with pulmonary arterial hypertension and dyspnoea resulting in a distribution of NYHA classes skewed towards the higher classes.

The overall level of disability as identified by the HAQ in our European SSc population is > 4 times higher than that reported in the general French population, and comparable to that reported in other systemic rheumatic diseases

[2, 38, 39]. The HAQ score observed in our cohort is similar to that found in other SSc studies, with about half of patients considering themselves to be mildly to moderately disabled [14, 18]. However, the SHAQ scores as well as the VASs encompassed in it are lower in our study than in a French single-centre study [29]. This discordance might be explained by the lower percentage of dcSSc patients in our population.

In patients with dcSSc the level of disability was significantly higher than in patients with limited SSc. The differences between SSc subsets in our cohort were, however, smaller than those reported previously in much smaller studies [13, 18, 29]. Interestingly, the main factors contributing to disability, namely dyspnoea, gastrointestinal symptoms, muscle weakness, DUs and pain, were similar in the SSc subsets. This goes in line with a recent survey by Frantz *et al*. [22] that identified no difference of patient-perceived impact of organ involvement on QoL between SSc subsets.

There are limitations of our study. We only had SHAQ data of about 45% of all eligible patients. A selection bias might have occurred in both directions, that is, patients with more severe disease may have felt too unwell to fill in the SHAQ questionnaire, or were actually more likely to fill in the questionnaire as they felt more impaired. The demographic characteristics of the patients included in this study were, however, comparable to the DeSScipher patients without an available SHAQ, as were the disease duration and the distribution of the SSc subsets. One problem often arising in observational studies is the data quality. However, one big strength of the DeSScipher cohort is that there were various strategies in place to enhance data quality, including on-site data monitoring. Thus, our results are likely to better reflect the bigger SSc community than those of previous studies, particularly due to the multicentre and multinational nature of this study.

In conclusion, this study demonstrates significantly impaired functional capacity in a large proportion of SSc patients, and demonstrates that dyspnoea, pain, DUs, muscle weakness and gastrointestinal symptoms are the most important contributors perceived by the patients. Our finding that objective measures are not associated with patient-perceived disability is a clarion call to researchers and clinicians that the many and multi-faceted aetiologies of disability in SSc are poorly understood. Further, the root causes impacting disability are likely overlooked and poorly assessed in the clinical setting. As a result of this, QoL is not yet targeted by our treatment armamentarium.

Acknowledgements

This study was carried out on behalf of the DeSScipher Consortium and contributing EUSTAR centres. EUSTAR acknowledges the unconditional support that EULAR has provided in the past for the maintenance of the EUSTAR database and the EUSTAR secretariat.

Funding: This study, as part of the DeSScipher project, was supported by the European Community's Framework Programme 7 [FP7-HEALTH-2012.2.4.4-2 – Observational trials in rare diseases; grant agreement No. 305495].

Disclosure statement: D.H. received consultancies from Actelion, Switzerland. U.M.-L. is supported by the FP7 program of the European Commission. N.H. has received lecture fees and research support from Actelion and Bayer. Y.A. has received honoraria and/or research support/grants from Actelion, Bayer, Biogen, BMS, Genentech-Roche, Galapagos, Inventiva, Medac, Pfizer, Sanofi, Servier, Union Chimique Belge. O.D. had a consultancy relationship and/or has received research funding from 4 D Science, AbbVie, Actelion, Active Biotec, Bayer, BiogenIdec, Bristol-Myers Squibb, Boehringer Ingelheim, ChemomAb, EpiPharm, espeRare foundation, Genentech/Roche, GlaxoSmithKline, Inventiva, iQone Healthcare, Lilly, medac, Mepha, MedImmune, Pharmacyclics, Pfizer, Sanofi, Serodapharm and Sinoxa in the area of potential treatments of scleroderma and its complications. In addition, O.D. has a patent mir-29 for the treatment of systemic sclerosis licensed. V.L. received personal fees from the European Union Seventh Framework Program (FP7/2007-2013) during the conduct of the study. C.M. has received research support and/or honoraria and has/had consultancy relationship from Abbvie, Actelion, Genetech/Roche and Geneva Romfarm in the area of systemic sclerosis and its complications. B.M. had grant/research support from AbbVie, Protagen, EMDO and Novartis, congress support from Pfizer, Roche, Actelion and has a patent licensed for mir-29 for the treatment of systemic sclerosis. C.D. has received consultancy fees or honoraria from Actelion, Bayer, GSK, CSL Behring, Merck-Serono, Genentech-Roche, Inventiva, Sanofi-Aventis and Boehringer Ingelheim. All other authors have declared no conflicts of interest.

References

1 Hudson M, Thombs BD, Steele R *et al*. Health-related quality of life in systemic sclerosis: a systematic review. Arthritis Rheum 2009;61:1112–20.

2 Johnson SR, Glaman DD, Schentag CT, Lee P. Quality of life and functional status in systemic sclerosis compared to other rheumatic diseases. J Rheumatol 2006;33:1117–22.

3 Mouthon L, Mestre-Stanislas C, Berezne A *et al*. Impact of digital ulcers on disability and health-related quality of life in systemic sclerosis. Ann Rheum Dis 2010;69:214–7.

4 Kwakkenbos L, Jewett LR, Baron M *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:e003563.

5 Suarez-Almazor ME, Kallen MA, Roundtree AK, Mayes M. Disease and symptom burden in systemic sclerosis: a patient perspective. J Rheumatol 2007;34:1718–26.

6 Steen VD, Medsger TA. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 1997;40:1984–91.

7 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;53:256–62.

8 Pope J. Measures of systemic sclerosis (scleroderma): Health Assessment Questionnaire (HAQ) and Scleroderma HAQ (SHAQ), Physician- and Patient-Rated Global Assessments, Symptom Burden Index (SBI), University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Scale (UCLA SCTC GIT) 2.0, Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) (Mahler's Index), Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), and Raynaud's Condition Score (RCS). Arthritis Care Res 2011;63(Suppl 1):S98–S111.

9 Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). Clin Exp Rheumatol 2005;23(5 Suppl 39):S14–8.

10 Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol 2003;30:167–78.

11 Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health Qual Life Outcomes 2003;1:20.

12 Merkel PA, Herlyn K, Martin RW *et al*. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. Arthritis Rheum 2002;46:2410–20.

13 Smyth AE, MacGregor AJ, Mukerjee D *et al*. A cross-sectional comparison of three self-reported functional indices in scleroderma. Rheumatology 2003;42:732–8.

14 Racine M, Hudson M, Baron M, Nielson WR. The impact of pain and itch on functioning and health-related quality of life in systemic sclerosis: an exploratory study. J Pain Symptom Manage 2016;52:43–53.

15 Franck-Larsson K, Graf W, Rönnblom A. Lower gastrointestinal symptoms and quality of life in patients with systemic sclerosis: a population-based study. Eur J Gastroenterol Hepatol 2009;21:176–82.

16 Omair MA, Lee P. Effect of gastrointestinal manifestations on quality of life in 87 consecutive patients with systemic sclerosis. J Rheumatol 2012;39:992–6.

17 Hughes M, Snapir A, Wilkinson J *et al*. Prediction and impact of attacks of Raynaud's phenomenon, as judged by patient perception. Rheumatology 2015;54:1443–7.

18 Strickland G, Pauling J, Cavill C, McHugh N. Predictors of health-related quality of life and fatigue in systemic sclerosis: evaluation of the EuroQol-5D and FACIT-F assessment tools. Clin Rheumatol 2012;31:1215–22.

19 Chow S, Pope JE, Mehta S. Lack of correlation of the health assessment questionnaire disability index with lung parameters in systemic sclerosis associated pulmonary arterial hypertension. Clin Exp Rheumatol 2008;26:1012–7.

20 Lumetti F, Barone L, Alfieri C *et al*. Quality of life and functional disability in patients with interstitial lung disease related to Systemic Sclerosis. Acta Biomed 2015;86:142–8.

21 Guillevin L, Hunsche E, Denton CP *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.

22 Frantz C, Avouac J, Distler O *et al*. Impaired quality of life in systemic sclerosis and patient perception of the disease: a large international survey. Semin Arthritis Rheum 2016;46:115–23.

23 Frerix M, Abignano G, Allanore Y *et al*. SAT0467 The Five Prospective Observational Trials of the International Systemic Sclerosis FP7-Health Research Project Desscipher: A Interim Report. Ann Rheum Dis 2015;74(Suppl 2):829.3–30.

24 The DeSScipher Project. https://www.uni-giessen.de/fbz/fb11/institute/klinik/rheumatologie/desscipher-en (9 November 2015, date last accessed).

25 Walker UA, Tyndall A, Czirják L *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;66:754–63.

26 Meier FMP, Frommer KW, Dinser R *et al*. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 2012;71:1355–60.

27 van den Hoogen F, Khanna D, Fransen J *et al*. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737–47.

28 Masi AT, Rodnan GP, Medsger TA Jr *et al*. 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;23:581–90.

29 Georges C, Chassany O, Mouthon L *et al*. Validation of French version of the Scleroderma Health Assessment Questionnaire (SSc HAQ). Clin Rheumatol 2005;24:3–10.

30 Sterne J, White IR, Carlin JB *et al*. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393.

31 Carpenter JR, Kenward MG. Multiple Imputation and its Application, 1st edn. Chichester: John Wiley & Sons, 2013.

32 Wells GA, Tugwell P, Kraag GR *et al*. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol 1993;20:557–60.

33 Dworkin RH, Turk DC, Wyrwich KW *et al*. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–21.

34 Strand V, Smolen JS, van Vollenhoven RF *et al*. Certolizumab pegol plus methotrexate provides broad relief from the burden of rheumatoid arthritis: analysis of patient-reported outcomes from the RAPID 2 trial. Ann Rheum Dis 2011;70:996–1002.

35 Brand M, Hollaender R, Rosenberg D *et al*. An observational cohort study of patients with newly diagnosed digital

ulcer disease secondary to systemic sclerosis registered in the EUSTAR database. Clin Exp Rheumatol 2015;33(4 Suppl 91):S47–54.

36 Lóránd V, Czirják L, Minier T. Musculoskeletal involvement in systemic sclerosis. Presse Med 2014;43:e315–28.

37 Bassel M, Hudson M, Taillefer SS *et al*. Frequency and impact of symptoms experienced by patients with systemic sclerosis: results from a Canadian National Survey. Rheumatology 2011;50:762–7.

38 Loos-Ayav C, Chau N, Riani C, Guillemin F. Functional disability in France and its relationship with health-related quality of life – a population-based prevalence study. Clin Exp Rheumatol 2007;25:701–8.

39 Oude Voshaar MAH, ten Klooster PM, Taal E *et al*. Linking physical function outcomes in rheumatology: Performance of a Crosswalk for Converting Health Assessment Questionnaire Scores to Short Form 36 Physical Functioning Scale Scores. Arthritis Care Res 2014;66:1754–8.

Clinical vignette

Rheumatology 2018;57:450
doi:10.1093/rheumatology/kex297
Advance Access publication 9 August 2017

Cocaine-induced periostitis and vasculopathy

A 46-year-old male patient with ongoing history of cocaine abuse presented with bilateral pain in the anterior thigh. The patient's skin, spine and joints were normal. The muscles of the thigh displayed normal force and no tenderness on palpation. Blood work showed elevated ESR (46 mm/h), CRP [168 mg/l (normal <5 mg/l], and creatine phosphokinase [352 U/l (normal <190 U/l)]. Leucocytes and granulocytes were slightly elevated. Urinalysis showed a non-glomerular microhaematuria (Fig. 1).

The MRI of both thighs detected a circular bilateral periostitis. The visceral angiogram showed a vasculopathy of the small and very small vessels of the spleen and liver and bilateral partial kidney infarction. There were no microaneurisms. Chest radiographs and echocardiography were normal and ANCA was negative. We made the diagnosis of cocaine-induced periostitis and small-vessel vasculopathy and the patient was started on oral corticosteroids (50 mg/day) and acetic acid 100 mg/day, which led to rapid improvement.

Cocaine is well known to be able to induce vasculitic reactions, resembling idiopathic granulomatosis with polyangiitis, sometimes including positive ANCA. In contrast, a non-inflammatory syndrome with vasoconstriction, arterial stenoses and aneurisms is also known [1].

The periostitis in our patient may be a sign of cocaine-induced vasculitis, as periostitis has been described rarely in other systemic vasculitides [2]. However, it may also be the result of exposure to the cocaine adulterant levamisole, as we know about the possible occurrence of periostitis with prolonged antifungal treatment with voriconazole (an imidazole like levamisole).

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

Ralph Melzer[1] and Lukas Schmid[1]

[1]*Rheumatology, Luzerner Kantonsspital, Lucerne, Switzerland*

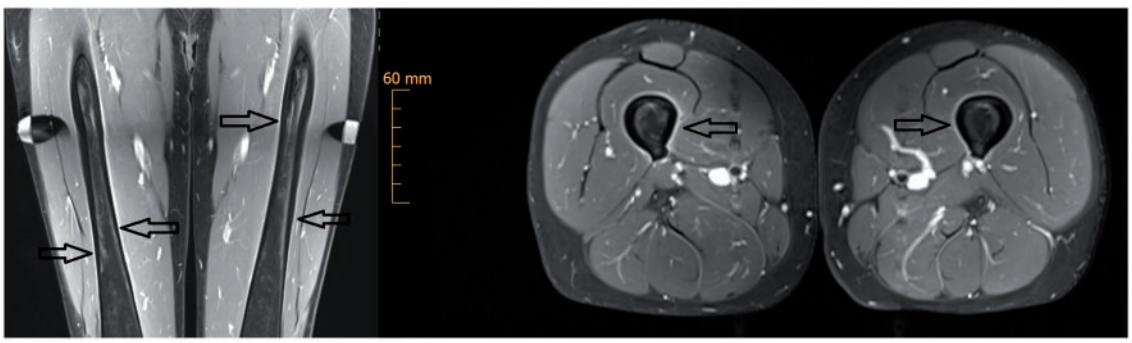
Correspondence to: Ralph Melzer, Rheumatology, Luzerner Kantonsspital, Spitalstrasse, 6000 Lucerne, Switzerland.
E-mail: ralph.melzer@luks.ch

References

1 Graf J. Rheumatic manifestations of cocaine use. Curr Opin Rheumatol 2013;25:50–5.

2 Périchon S, Pagnoux C, Seror R *et al*. Periostitis in systemic necrotizing vasculitides: study of the 4 cases identified among 1762 patients of the FVSG database and review of the literature. Presse Med 2010;39:165–73.

Fig. 1 Gadolinium-enhanced, T1-weighted, fat-saturated MRI



Bilateral circumferential periostitis (arrows) of the femoral diaphysis in the transverse and frontal planes.