Diagnostic measures for patients with systemic sclerosis-associated myopathy

R. Baumberger[1], S. Jordan[1], O. Distler[1], P. Baschung Pfister[2], B. Maurer[3]

[1]Department of Rheumatology, University Hospital Zurich;
[2]Directorate of Research and Education, Physiotherapy Occupational Therapy Research Centre, University Hospital Zurich;
[3]Department of Rheumatology and Immunology, University Hospital Bern, Switzerland.

Regina Baumberger, MM
Suzana Jordan, PhD
Oliver Distler, MD, Prof.
Pierrette Baschung Pfister, PhD
Britta Maurer, MD

Please address correspondence to
Britta Maurer,
Department of Rheumatology and Immunology,
University Hospital Bern,
Freiburgstrasse 16p,
3010 Bern, Switzerland.
E-mail: britta.maurer@insel.ch

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ORCID iD
R. Baumberger: 0000-0001-5979-1271
S. Jordan: 0000-0002-8114-8239
O. Distler: 0000-0002-0546-8310
P. Baschung Pfister: 0000-0002-4930-2435
B. Maurer: 0000-0001-9385-8097

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ABSTRACT

Objective. *To evaluate the clinico-serological profile and to assess diagnostic parameters of myopathy in patients with systemic sclerosis (SSc)-associated myopathy.*

Methods. *We explored the profiles of SSc-myopathy patients and matched non-myopathy SSc patients as well as different diagnostic measures for muscle affection. Additionally, the muscle performance of SSc-myopathy patients, assessed by the Manual Muscle Test for 8 muscle groups (MMT-8) and the Functional Index-2 (FI-2), was compared with that of patients with primary myositis.*

Results. *In SSc-myopathy patients, the following features occurred significantly more often even after Bonferroni correction for multiple comparisons: immunosuppressive treatment (56.0% vs. 24.1%; p=0.0003), elevated levels of creatine kinase (CK) (48.3% vs. 5.3%, p<0.0001), anti-PM-Scl antibodies (30.4% vs. 4%, p=0.00048), and absence of RNA Polymerase III antibodies (7.3% vs. 28.3%, p<0.0001). The MMT-8 showed a mild muscle weakness in SSc-myopathy as well as in primary myositis patients with similar age and sex. Muscle endurance tested by the FI-2 was generally compromised in both cohorts, yet the distribution pattern of affected muscle groups differed between the two cohorts.*

Conclusion. *We confirmed previously described clinic-serological characteristics of SSc-myopathy patients. Our study suggests that autoantibody profile and CK levels may be helpful in establishing the diagnosis of SSc-myopathy. Whole-body MRI might be more accurate to capture the disease extent than MRI of selected muscle groups. Functional muscle tests validated for primary myositis did not perform well for the assessment of muscle function in patients with SSc-myopathy. Both, potential confounders such as skin, joint, and cardiovascular involvement as well as lack of sensitivity might have negatively affected the test performance in this population.*

Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease which is characterised by immune dysregulation, endothelial cell dysfunction followed by defective vascular repair and neovascularisation, and progressive tissue fibrosis of the skin and internal organs (1). Myopathy is a frequent, yet poorly investigated and understood phenomenon in patients with systemic sclerosis although it might cause substantial morbidity and is associated with a poor prognosis (2). Since there exist no diagnostic consensus criteria for myopathy in SSc, its prevalence varies widely (6–90%) in the literature (2, 3). In order to improve this lack of diagnostic consensus criteria and diagnostic tools, a SSc-myopathy sub-cohort of the European Scleroderma Trials and Research group (EUSTAR) (4) cohort has been established in 2015 within the context of the "EUSTAR-Scleroderma clinical trial and research consortium (SCTC) sub-cohort initiative" (5).

The clinical presentation of SSc-associated myopathy is highly heterogeneous ranging from mild myalgia and a slight elevation of muscle enzymes to severe muscle weakness. The increased mortality can mainly be attributed to cardiac involvement, *i.e.* left ventricular dysfunction, arrhythmias, conduction blocks, and myocarditis (6-8). To diagnose SSc-related myopathy, most often a combination of muscle weakness as the most prominent clinical feature, elevation of muscle enzymes, pathological findings on electromyogram (EMG), magnetic resonance imaging (MRI) or muscle biopsies are used. Moreover, a positive association

has been reported between SSc-myopathy and several auto-antibodies including anti-PM-Scl, anti-topoisomerase-1, anti-Ku, anti-U3-RNP, anti-U1-RNP, anti-Jo, and anti-RuvBL1/2 (9-14). In contrast, anti-centromere- and anti-RNA-Polymerase III-antibodies in some studies were reported to be negatively associated (6-12).

Muscle weakness needs to be verified by the treating physician or physiotherapist. The Manual Muscle Test for 8 muscle groups (MMT-8) and the Functional Index-2 (FI-2) are commonly used and validated tests for patients with primary myositis to evaluate muscle weakness and endurance, respectively (15, 16). Inflammatory myopathies are a rare and heterogeneous group of multi-system autoimmune diseases and encompass polymyositis, dermatomyositis, juvenile dermatomyositis, inclusion body myositis, immune-mediated necrotising myopathy, and the antisynthetase syndrome (17). In addition to the typically proximally and symmetrically distributed skeletal muscle involvement, other organs such as the skin and the lung can be affected, depending on the underlying disease. In SSc-myopathy, so far no data on the suitability of these tests for the assessment of muscle involvement are available.

We therefore wanted to evaluate diagnostic measures in patients with SSc-associated myopathy. In particular, we focused on the diagnostic performance of muscle function tests compared with patients with primary myositis in our respective local cohorts.

Materials and methods

Patients and study design

The SSc cohort of the Department of Rheumatology, University Hospital Zurich (USZ), Switzerland, was evaluated for this retrospective data analysis, which comprises patients with established diagnosis of SSc meeting the American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) classification criteria (18).

The SSc-myopathy sub-cohort has been established in 2015 within the context of the "EUSTAR-SCTC initiative" (EULAR Scleroderma Trials and Research group - Scleroderma Clinical Trials Consortium) by extending the EUSTAR MEDS online (Minimal Essential Data Set) (19) for myositis-related items. These include 10 questions concerning the medical history, 4 clinical exams, 25 laboratory parameters, and 3 diagnostic tools. For detailed information, refer to the online supplement. For enrolment, at least one of the following inclusion criteria needs to be met: elevated levels of serum muscle enzymes (creatine kinase (CK) or aldolase), proximal muscle weakness judged by the treating physician or physiotherapist, muscle atrophy on physical examination, or positive myositis-associated autoantibodies (Jo-1, PM-Scl, U1-RNP, Ku, Mi-2, SRP, PL-7, PL-12, OJ, EJ, p155/140, MDA5, MXP2).

SSc-myopathy patients were matched to and compared with non-myopathy SSc patients in a 1:1 ratio for the main SSc features. Matching criteria were age, gender, extent of skin involvement according to the Le Roy classification (20), disease duration > or ≤ than 5 years and presence of the main SSc auto-antibodies (anti-centromere, anti-topoisomerase-1, anti-RNA polymerase III) (21) (Supplementary Table S1).

Myopathy-related characteristics were assessed at one-year follow-up. To compare the muscle function of patients with SSc-associated myopathy with that of patients with primary myositis, patients of the local myositis cohort of the USZ being part of the Euromyositis registry (17), an international data registry for myositis patients, were included. Data were collected from the institutional electronic patients' charts. Written informed consent was obtained from all the patients. The study was approved by the local ethics committee (KEK-ZH-Nr. 2012-0419, pre-BASEC- EK-839, BASEC KEK-Nr.-2016-01515).

MMT8 and FI-2

MMT8 and FI-2 tests were performed as previously described (15, 16, 22). The MMT-8 is scored from 0 to 10 and measures the muscle weakness of 8 different muscle groups (M. deltoideus, M. biceps, wrist extensors, M. quadriceps, ankle dorsiflexors, neck flexors, M. gluteus maximus and medius), which are most commonly affected in primary myositis (22). Scores between 0–3, 4–6 and 7–9 are defined as severe, moderate and mild muscle weakness, respectively and a score of 10 indicates absence of muscle weakness. The total score representing the sum of the single scores varies from 0 to 80 (0=no muscle contraction, 0–31=severe muscle weakness, 32–55=moderate muscle weakness, 56–79=mild muscle weakness, 80=normal strength). The FI-2 examines the muscle endurance based on repetitive movements with a predefined maximum of 60 (shoulder flexion, shoulder abduction, head lift, hip flexion, step test) and 120 (heel and toe lift) repetitions, respectively (15). The results were presented as the percentage of the maximal repetitions per muscle group. All patients were tested and supervised by the same two well experienced examiners (P.B. 25 years of experience / I.S. 13 years of experience). To further address potential differences in the distribution of muscle affection, we analysed the available MRI scans of the SSc-myopathy patients.

Statistical analysis

SPSS version 25 was employed for the statistical analysis. Frequencies and percentages as well as medians, first and third quartiles (Q1, Q3) were reported for categorical and continuous variables, respectively. Binary logistic regression was performed for the propensity score matching (PSM). The closest PSM score was used to match the SSc-myopathy patients with non-myopathy SSc patients. Statistical analysis between two groups of related variables was performed using McNemar or in case of more than one variable marginal homogeneity test for categorical variables and Wilcoxon signed rank test for continuous variables. For independent variables, Chi-square test was used for categorical variables and Mann-Whitney U-test for continuous variables. To minimise the probability of committing a type 1 error (α) due to multiple testing, Bonferroni correction (α/number of tests) was applied and thus only p-values <0.000595 (0.05/84) were considered as statistically significant.

Results

Characteristics and distinguishing features of SSc-myopathy patients

Out of the entire local SSc cohort (n=454) at the time of the first data export (8 October 2018), 58 patients fulfilled the myopathy inclusion criteria and were compared to 58 matched non-myopathy SSc patients. The majority of patients (74.1%) was female, the median age was 60 years and the median disease duration was 77.0 months in the myopathy cohort and 69.6 months in the non-myopathy cohort. (Table I).

About the same percentage of patients in both cohorts suffered from joint synovitis, renal crisis and lung fibrosis. Moreover, no significant difference was found for the presence of anti-nuclear antibodies, the elevation of C-reactive protein, aspartate transaminase, and alanine transaminase (Table II).

The active disease score defined by Valentini (23) was higher in the SSc-myopathy cohort than in the SSc-non-myopathy cohort. More patients with myopathy had scleredema and more than twice as many had tendon friction rubs. Joint contractures, on the other hand, were found more frequently in non-myopathy SSc patients compared to SSc-myopathy patients. In accordance with the higher disease activity, significantly more patients with myopathy were prescribed an immunosuppressive treatment (56.0% *vs*. 24.1%, p=0.0003). Remarkably, in one third of patients with myopathy receiving an immunosuppressive therapy (11/33 (33.3%)), the treatment was prescribed because of muscle involvement as the only indication or one out of several indications (mostly lung fibrosis and joint synovitis).

The prevalence of active digital ulcers was higher in the SSc-non-myopathy cohort. Furthermore, there was a tendency towards a late SSc pattern in the nailfold capillaroscopy and a higher prevalence of pulmonary hypertension in patients without myopathy (Table I).

We observed an association between specific autoantibodies and SSc-associated myopathy. Anti-PM-Scl antibodies were found significantly more often in the SSc-myopathy cohort compared with non-myopathy SSc pa-

Table I. Description of matched SSc patients with and without myopathy at baseline (clinical parameters).

Characteristics	Patients with myopathy		Patients without myopathy		p-value
Sex					
Female	43/58	(74.1)	43/58	(74.1)	-
Male	15/58	(25.9)	15/58	(25.9)	-
Age (years)	59.7	(49.0, 68.3)	59.9	(48.4, 68.6)	-
Disease duration (months) [1]	77.0	(34.8, 141.1)	69.6	(38.4, 145.3)	-
Extent of skin involvement [2]					
Limited cutaneous involvement	37/58	(64.9)	38/58	(65.5)	-
Diffuse cutaneous involvement	18/58	(31.6)	18/58	(31.0)	-
Systemic Sclerosis sine scleroderma	3/58	(3.5)	2/58	(3.4)	-
mRSS	2.5	(0.0, 9.3; n=58)	6.0	(0.5, 11.8; n=56)	0.183
Scleredema	48/57	(84.2)	32/53	(60.4)	0.036
Pitting scars on fingertips	25/56	(44.6)	22/55	(40)	0.629
Gangrene	0/57	(0)	0/55	(0)	-
Digital ulcers (active)	4/56	(7.1)	13/57	(22.8)	0.049
Digital ulcers (ever)	22/56	(39.3)	23/57	(40.4)	1.000
Raynaud›s phenomenon	51/58	(87.9)	55/58	(94.8)	0.289
Teleangiectasia	33/57	(57.9)	32/51	(62.7)	0.690
Nailfold capillaroscopy: Scleroderma pattern					
early	5/43	(11.8)	2/35	(5.7)	0.375
active	18/43	(41.9)	12/35	(34.3)	0.549
late	20/43	(46.5)	21/35	(60)	0.180
Active disease score (VAI)	3.25	(2.25, 5.00; n=53)	2.92	(1.44, 3.78; n=34)	0.166
Active disease score (VAI>=3)	14/58	(24.1)	4/58	(6.9)	0.013
Immunosuppressive treatment [3]	33/58	(56.9)	14/58	(24.1)	0.0003*
Immunosuppresive treatment due to muskuloskeletal involvement (exclusively or amongst other causes)	11/33	(33.3%)	-		-
Organ involvement					
Muscle weakness	18/57	(31.6)	6/58	(10.3)	0.011
Muscle atrophy	7/57	(12.3)	2/58	(3.4)	0.180
Joint synovitis [4]	10/58	(17.2)	8/58	(13.8)	0.791
Joint contractures	17/57	(29.8)	26/58	(44.8)	0.134
Tendon friction rubs	9/56	(16.1)	4/58	(6.9)	0.180
Dyspnoea (NYHA ≤2)	51/57	(89.5)	43/50	(86)	0.549
Dyspnea (NYHA >2)	6/57	(10.5)	7/50	(14)	0.549
Lung fibrosis on HRCT	33/58	(56.9)	25/45	(55.6)	0.412
DLCO/VA	74.0	(63, 83; n=43)	79.5	(65 88; n=26)	0.268
FVC (%)	96.0	(82.3, 110.8; n=56)	93.0	(84, 108; n=49)	0.848
FEV1 (%)	92.0	(79.5, 106.8; n=56)	89.0	(77.5, 103.0; n=49)	0.938
TLC (%)	95.0	(85, 113; n=55)	101.5	(83.5, 113.5; n=48)	0.146
Renal crisis	3/58	(5.2)	4/58	(6.9)	1.000
Cardiac arrhythmias	11/58	(19)	6/58	(10.3)	0.302
Pericarditis / Myocarditis	1/58	(1.7)	0/58	(0)	1.000
Pulmonary hypertension	3/57	(5.3)	9/51	(17.6)	0.057
Diastolic function abnormal	14/55	(25.5)	19/57	(33.3)	0.648
Proximal Dysphagia	18/58	(31)	12/58	(20.7)	0.289

For nominal variables, the absolute and relative frequencies are shown: n/total valid cases (%).
Continuous variables are described as median and 1st, 3rd quartiles (Q1, Q3).
Data for some clinical and laboratory parameters were available for fewer patients than the total number of patients in the respective group.
*Denotes statistical significance after Bonferroni correction for multiple comparisons.
[1]Disease duration was calculated as difference between the date of the baseline visit and the date of the first non-Raynaud's symptom of the disease, as reported by the patients.
[2]Extent of skin involvement as defined by LeRoy criteria.
[3]The "early scleroderma pattern" in the nailfold capillaroscopy is characterised by few enlarged/giant capillaries, few capillary haemorrhages, relatively well-preserved capillary distribution, and no evident loss of capillaries as described by Cutolo *et al*. (40).
[4]The "active scleroderma pattern" in the nailfold capillaroscopy is characterised by frequent giant capillaries, frequent capillary haemorrhages, moderate loss of capillaries, mild disorganisation of the capillary architecture, and absent or mild ramified capillaries as described by Cutolo *et al*. (40).
[5]The "late scleroderma pattern" in the nailfold capillaroscopy was characterised by irregular enlargement of the capillaries, few or absent giant capillaries and haemorrhages, severe loss of capillaries with extensive avascular areas, disorganisation of the normal capillary array, and ramified/bushy capillaries as described by Cutolo *et al*. (40).
[6]Immunosuppressive treatment in patients with myopathy: prednisone, methotrexate, mycophenolate cyclophosphamide, azathioprine, rituximab, tocilizumab; immunosuppressive treatment in patients without myopathy: prednisone, methotrexate, mycophenolate, rituximab, tocilizumab, anti-TNF (tumour necrosis factor alpha) inhibitors.
[7]Joint synovitis was defined as swelling of the joints as judged by the treating physician.
DLCO/VA: diffusing capacity of the lung for carbon monoxide divided by the alveolar volume; FEV1: forced expiratory volume at 1 second; FVC: forced vital capacity; HRCT: high resolution computer tomography; mRSS: modified Rodnan skin score; NYHA: New York Heart Association; TLC: total lung capacity; VAI: Valentini Activity Index.

Table II. Description of matched SSc patients with and without myopathy at baseline (laboratory parameters).

Characteristics	Patietients with myopathy	Patients without myopathy	*p*-value
Immunological profile			
ANA	58/58 (100)	58/58 (100)	1.000
ACA	16/57 (28.1)	16/58 (27.6)	0.754
Antitopoisomerase-I antibodies	15/58 (25.9)	12/58 (20.7)	0.607
Anti-U1-RNP	7/56 (12.5)	2/49 (4.1)	0.289
Anti-RNA Polymerase III	4/55 (7.27)	15/53 (28.3)	0.006
Anti-PM-Scl	17/56 (30.4)	2/50 (4)	0.00048*
Anti-Ku	4/52 (7.7)	1/37 (2.7)	0.625
Anti-U3-RNP	1/45 (2.2)	2/32 (6.3)	1.000
Anti-Jo-1	0/46 (0)	0/18 (0)	-
Anti-Mi-2	0/42 (0)	0/14 (0)	-
Anti-SRP	0/26 (0)	0/3 (0)	-
Anti-PL-7	0/27 (0)	0/4 (0)	-
Anti-PL-12	0/26 (0)	0/4 (0)	-
Anti-HMGCR	0/2 (0)	0/2 (0)	-
Laboratory tests			
CRP elevation	12/58 (20.7)	11/57 (19.3)	1.000
CK elevation	28/58 (48.3)	3/57 (5.3)	<0.0001*
CK (U/l)	137.0 (71.5, 245.0; n=58)	80.0 (59.0, 111.0; n=51)	<0.0001*
NTproBNP (pg/ml)	124.0 (59.3, 355.5; n=56)	125.0 (68.0, 290.5; n=49)	0.824
Troponin-T elevation	18/54 (33.3)	6/37 (16.2)	0.021
Troponin-T ≥50 (pg/ml)	12/17 (70.6)	2/6 (33.33)	0.268
AST elevation	8/56 (14.3)	8/55 (14.5)	1.000
ALT elevation	1/34 (2.9)	3/34 (8.8)	1.000
LDH elevation	17/54 (31.5)	10/52 (19.2)	0.167

For nominal variables, the absolute and relative frequencies are shown: n/total valid cases (%).
Continuous variables are described as median and 1st, 3rd quartiles (Q1, Q3).
Data for some clinical and laboratory parameters were available for fewer patients than the total number of patients in the respective group.
*Denotes statistical significance after Bonferroni correction for multiple comparisons.
ACA: anticentromere antibodies; ALT: alanine aminotransferase; ANA: antinuclear antibodies; Anti-HMGCR: anti-HMG-CoA-reductase antibodies; Anti-U3-RNP: anti-fibrillarin antibodies; AST: aspartate aminotransferase; CK: creatine kinase; CRP: C reactive protein; LDH: lactate dehydrogenase; NTproBNP: N-terminal pro brain natriuretic peptide; RNP: ribonucleoprotein.

tients (30.4% *vs*. 4%, p=0.00048) and RNA Polymerase III antibodies less often. Furthermore, our results show a tendency towards a higher prevalence of anti-U1snRNP-antibodies in SSc-myopathy patients. Antibodies indicative of primary myositis such as anti-Jo-1, anti-Mi-2, anti-SRP, anti-PL-7, anti-PL-12, and anti-HMGCR were not present in either SSc cohort.

Moreover, there was a tendency towards a higher prevalence of dysphagia and cardiac arrhythmias in the SSc-myopathy cohort compared to the SSc-cohort without myopathy. Troponin T was more often elevated in the SSc-myopathy cohort (33.3% *vs*. 16.2%).

CK was significantly more often elevated in SSc-myopathy patients (48.3% *vs*. 5.3%, p<0.0001) and showed significantly higher, albeit moderately elevated levels. Correspondingly, the lactate dehydrogenase (LDH) level was more often elevated in the SSc-myopathy cohort (Table II).

Out of the 58 SSc-myopathy patients, 35 were eligible for the annual follow-up visit. After one-year of follow-up, they showed a tendency towards a decrease in overall disease activity (Table III). Skeletal muscle involvement, *i.e*., muscle weakness and muscle atrophy, as well as heart involvement became less, supported by a reduced frequency of CK and troponin-T elevations ≥ 50pg/ml. There were no significant differences between the SSc-myopathy patients, who were available and the SSc-myopathy patients who were not available for the annual follow-up visit.

Characteristics of primary myositis patients

At the time point of data extraction, the local myositis cohort of the Department of Rheumatology of the USZ included 159 patients with primary myositis (dermatomyositis, polymyositis, antisynthetase syndrome, overlap syndrome, associated myositis, unclassified autoimmune myositis), out of which 35 patients had available data for MMT-8 and FI-2 and thus qualified for our study.

Seventy-four percent of the included myositis patients were female, the median age was 59 years. The most common subtype of myositis was dermatomyositis (45.7%), followed by polymyositis (25.7%), and antisynthetase syndrome (11.4%). The remaining 14.4% suffered either from an unclassified autoimmune myositis, an overlap syndrome or from a secondary myositis. CK was elevated in 24.1% of all patients. The majority of the patients (54%) had a normal nailfold capillaroscopy. The most common autoantibodies were antinuclear antibodies, followed by anti-SSA and anti-Jo-1 (Table IV).

Muscle weakness and endurance in SSc-myopathy and primary myositis patients

Thirty-four patients of the SSc-myopathy sub-cohort with available data for MMT-8 and FI-2 were compared to 35 patients with primary myositis. Age (median 58.0, IQR 48.7–69.5 in SSc-myopathy *vs*. median 59.0, IQR 51.0–65.0 in primary myositis) and gender (26.5% female in SSc-myopathy *vs*. 25.0% female in myositis) were comparable (Table V).

As measured by the MMT-8 total score, both groups showed a mild muscle weakness without a significant difference between the two groups (Table V). In contrast, the analysis of the FI-2 showed a reduced muscle endurance in all tested muscles groups in both cohorts. SSc-myopathy patients showed the worst performance in the tasks head lift, heel lift and toe lift, whereas patients with primary myositis had the greatest difficulties performing step test, hip flexion, and head lift. The neck musculature was badly affected in both groups, however, the myositis patients showed even worse performance in the task head lift than the SSc-myopathy patients. In contrast, the SSc-myopathy patients performed worse than the

Table III. Description of SSc myopathy patients at baseline and follow-up.

Characteristics	Baseline (n=58)	Patients with follow-up at baseline (n=35)	Patients without follow-up at baseline (n=23)	*p*-value[1]	Follow-up (n=35)	*p*-value[2]
mRSS	2.5 (0.0, 9.25; n=57)	3.0 (0.3, 10.5; n=35)	2.0 (0.5, 6.5; n=23)	0.361	2.0 (0.0, 9.0; n=35)	0.041
Active disease Score	3.25 (2.25, 5.00; n=53)	3.3 (0.3, 5.3, n=34)	3.3 (2.3, 4.2; n= 19)	0.191	2.59 (1.00, 3.50; n=35)	0.109
Active disease Score ≥3	29/53 (54.7)	19/34 (55.9)	10/19 (52.6)	0.298	17/35 (48.6)	0.227
Organ involvement						
Muscle weakness	18/57 (31.6)	14/35 (40.0)	4/22 (18.18)	0.027	10/35 (28.6)	0.344
Muscle atrophy	7/57 (12.3)	4/35 (11.4)	3/22 (13.6)	0.808	3/35 (8.6)	1.000
Joint synovitis [3]	10/58 (17.2)	6/35 (17.1)	4/23 (17.4)	0.404	8/35 (22.9)	1.000
Joint contractures	17/57 (29.8)	10/35 (28.6)	7/22 (31.8)	0.320	15/35 (42.9)	0.146
Tendon friction rubs	9/56 (16.1)	6/35 (17.1)	3/21 (14.3)	0.602	4/35 (11.4)	0.727
Cardiac arrhythmias	11/58 (19)	8/35 (22.9)	3/23 (13.0)	0.062	6/34 (17.6)	0.250
Pericarditis / Myocarditis	1/58 (1.7)	1/35 (2.9)	0/23 (0.0)	-	0/32 (0.0)	1.000
Laboratory tests						
CRP elevation	12/58 (20.7)	9/35 (25.71)	3/23 (13.04)	0.164	12/35 (34.3)	0.508
CK elevation	28/58 (48.3)	16/35 (45.71)	12/23 (52.17)	0.534	9/35 (25.7)	0.016
AST elevation	8/56 (14.3)	3/34 (8.82)	5/22 (22.73)	0.024	2/32 (6.3)	1.000
ALT elevation	1/34 (2.9)	0/24 (0)	1/10 (10.0)	-	1/15 (6.7)	1.000
LDH elevation	17/54 (31.5)	13/33 (39.4)	4/21 (19.1)	0.050	6/32 (18.8)	0.070
Troponin-T elevation	18/54 (33.3)	11/31 (35.5)	7/23 (30.4)	0.918	10/30 (33.3)	1.000
Troponin-T ≥50 (pg/ml)	12/17 (70.6)	9/10 (90.0)	3/7 (42.9)	0.164	4/10 (40)	0.250
Immunosuppressive treatment [4]	33/58 (56.9)	23/35 (65.7)	10/23 (43.5)	0.025	18/35 (51.4)	0.125
Physical therapy	38/58 (65.5)	25/35 (71.4)	13/23 (56.5)	0.114	20/34 (58.8)	0.289

For nominal variables, the absolute and relative frequencies are shown: n/total valid cases (%). Continuous variables are described as median and 1st, 3rd quartiles (Q1, Q3).
Data for some clinical and laboratory parameters were available for fewer patients than the total number of patients in the respective group.
[1]*p*-value for comparison between patients with and without follow-up at baseline.
[2]*p*-value for comparison between all patients available at baseline and follow up.
[3]Joint synovitis was defined as swelling of the joints as judged by the treating physician.
[4]Immunosuppressive treatment at baseline: Prednisone, methotrexate, mycophenolate cyclophosphamide, azathioprine, rituximab, tocilizumab; Immunosuppressive treatment at one-year follow-up: Prednisone, methotrexate, mycophenolate, rituximab, tocilizumab.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; CRP: C reactive protein; LDH: lactate dehydrogenase; mRSS: modified Rodnan skin score.

myositis patients in the task shoulder abduction. The perceived exertion on the Borg CR10 Scale as indicator of patients' performance (15) was similar between both groups ensuring the comparability of the results. Our findings suggested a different involvement of muscle groups between the two cohorts, showing predominant affection of the distal leg musculature and the neck musculature in SSc-myopathy patients and predominant affection of the proximal leg and hip musculature as well as the neck musculature in myositis patients. It should, however, be taken into consideration that 11 of the 31 SSc-myopathy patients, who performed the tasks heel lift and toe lift suffered from joint contractures, 5 suffered from joint synovitis and 12 had an mRSS of the lower legs and feet between 1 and 3, indicating mild to severe skin thickening.

Sixteen patients of the SSc-myopathy cohort had undergone MRI. Six of these patients showed radiological signs of muscle affection. While affection of the shoulder girdle and of proximal leg musculature were found in 5 out of 6 patients the musculature of the distal legs and of the hands show affection in 2 out of 6 and in 1 out of 6 patients, respectively. Figure 1 shows a representative MRI of a male SSc-myopathy patient.

Discussion

In our study, the SSc patients with myopathy had a higher disease activity score, a higher prevalence of inflammatory features such as scleredema and tendon friction rubs as well as a higher rate of prescribed immunosuppressive treatment than patients without myopathy. There exist no treatment recommendations for SSc-associated myopathy. In general, myopathy in patients with normal or mildly elevated CK levels and absence of inflammation on MRI or biopsy often remains untreated (24, 25), whereas higher CK levels, MRI or biopsy-proven inflammation often require corticosteroids or immunosuppressive drugs, for example methotrexate (26). In our study, in one third of patients with SSc-associated myopathy receiving immunosuppressive treatment, amongst other causes such as lung fibrosis and joint synovitis, the indication for immunosuppressive treatment was musculoskeletal involvement. The higher prevalence of cardiac arrhythmias and the higher levels of troponin-T in the SSc-myopathy cohort are in agreement with previous studies, which postulated a possible association between skeletal myositis and cardiac disease (8, 27).

CK levels were significantly more often elevated in SSc-myopathy patients than in non-myopathy patients. However, our subjects did not exhibit very high CK levels compared to most patients with primary myositis (28) potentially relating to lower muscle mass or differences in the severity or the pathophysiology of muscle remodelling. This is supported by the literature

Table IV. Characteristics of patients with primary myositis at baseline.

Sex		
Female	26/35	(74.3)
Male	9/35	(25.7)
Age (years)	59.0	(51.0, 65.0)
Diagnosis		
Polymyositis	9/35	(25.7)
Dermatomyositis	16/35	(45.7)
Antisynthetase syndrome	4/35	(11.4)
Unclassified autoimmune myositis	3/35	(8.6)
Overlap-syndrome (polymyositis and Sjögren)	1/35	(2.9)
Associated myositis (Sjögren's syndrome)	1/35	(2.9)
Associated myositis (Colitis ulcerosa)	1/35	(2.9)
Nailfold capillaroscopy		
normal	13/24	(54.2)
Organic microangiopathy (predominantly capillary loss)	7/24	(29.2%)s
Organic microangiopathy (predominantly dilated vessels, giant capillaries and microhaemorrhages)	4/24	(16.7%)
CK (U/l)	95.5	(59.3, 232.8)
LDH elevation	8/27	(29.6)
AST elevation	3/31	(9.7)
ALT elevation	3/30	(10.0)
CRP elevation	5/29	(17.2)
ANA	18/29	(62.1)
Anti-Jo-1	4/29	(13.8)
Anti-PL-7	0/29	(0)
Anti-PL-12	2/29	(6.9)
Anti-EJ	0/9	(0)
Anti-OJ	0/3	(0)
Anti-SRP	1/26	(3.8)
Anti-Pm-Scl	2/28	(7.1)
Anti-Mi-2	1/28	(3.6)
Anti-Ku	0/26	(0)
Anti-U1-RNP	0/25	(0)
Anti-U3-RNP	0/2	(0)
Anti-SSA	7/25	(28.0)
Anti-SSB	0/23	(0)
Anti-Zo	0/3	(0)
Anti-SAE	0/7	(0)
Anti-KS	0/2	(0)

For nominal variables, the absolute and relative frequencies are shown: n/total valid cases (%). Continuous variables are described as median and 1st, 3rd quartiles (Q1, Q3).
Data for some clinical and laboratory parameters were available for fewer patients than the total number of patients.
[1]Immunosuppressive treatment: prednisone, methotrexate, azathioprine, mycophenolate, rituximab, tacrolimus, hydroxychloroquine.
ACA: anticentromere antibodies; ALT: alanine aminotransferase; ANA: antinuclear antibodies; Anti-HMGCR: anti-HMG-CoA-reductase antibodies; Anti-SAE: anti-small ubiquitin like modifier activating enzyme heterodimer antibody; Anti-SRP: anti-signal recognition particle; Anti-SSA: anti-Ro antibodies; Anti-SSB: anti-La antibodies; Anti-U3-RNP: anti-Fibrillarin antibodies; AST: aspartate aminotransferase; CK: creatine kinase; CRP: C reactive protein; LDH: lactate dehydrogenase.

describing many different forms of histopathology in SSc-myopathy patients ranging from necrosis, inflammation and acute neurogenic atrophy (28) to interstitial and perivascular fibrosis (3, 29).

Interestingly, signs of microvascular damage such as digital ulcers, a late scleroderma pattern in the nailfold capillaroscopy (implying severe loss of capillaries with large avascular areas), and pulmonary hypertension were more prevalent in SSc patients without myopathy. Correspondingly, the majority of myositis patients had a normal nailfold capillaroscopy. Thus, our findings support a previous observation by Bahnsing *et al*. who reported that 57% of their SSc cohort suffered from pulmonary arterial hypertension, while none of their polymyositis-scleroderma-overlap subjects did (30).

At the one-year follow-up, the active disease score as well as the prevalence of tendon friction rubs and elevated CK had decreased, potentially related to the prescribed immunosuppressive treatment. Moreover, muscle weakness as well as muscle atrophy were less common after one year, an effect, which seems to support the added benefit of physical therapy.

The antibody pattern represented in our study cohort is, with one exception, consistent with previous studies with a predominance of anti-PM-Scl and anti-U1nRNP antibodies and rarity of RNA-Polymerase III antibodies in the SSc-myopathy patients (9, 12). However, in contradiction with earlier findings, ACA-antibodies were equally present in both cohorts, SSc patients with and without myopathy (6).

Although muscle weakness and reduced muscle endurance are features, which have a great impact on the everyday life as well as on the quality of life of SSc-myopathy patients (31), up to now there exist no standardised diagnostic tools, which enable their early recognition. This study is the first to analyse the muscle function of patients with SSc-associated myopathy in the clinical tests for muscle strength and endurance, *i.e*. MMT-8 and FI-2.

The total MMT-8 score revealed a comparably mild muscle weakness in the SSc-myopathy as well as in the myositis patients without differences in the performance of individually tested muscle groups. However, even though the MMT-8 is a reliable and time efficient tool to assess general muscle weakness in patients with primary myositis (16), the test has been described as being unable to differentiate between mild muscle weakness and normal muscle strength (32). Therefore, we hypothesise that the actual prevalence of muscle involvement in SSc might be higher than described in our study because mild muscle weakness might have remained undiscovered by the MMT-8. Since the MMT-8 has neither been evaluated in SSc patients with nor in SSc patients without associated myopathy, it remains unclear how skin fibrosis, concomitant contractures or arthritis, features that were present in our patient cohort, might additionally affect the test results (33). Additional sources of measurement error may be linked to diurnal effects, subject comprehension of the testing task, motor skill, state of arousal, level of

Table V. MMT-8 and FI-2.

Characteristics	SSc patients with myopathy (n=34)	Patients with primary myositis (n=35)	*p*-value
Sex			
Female	25/34 (73.5)	26/35 (74.3)	-
Male	9/34 (26.5)	9/35 (25.7)	-
Age (years)	58.0 (48.7, 69.5)	59.0 (51.0, 65.0)	-
MMT-8 (x/10)			
M. deltoideus	9.0 (7.0, 10.0; n=34)	9.0 (8.0, 10.0; n=35)	0.865
M. biceps	9.0 (9.0, 10.0; n=33)	10.0 (10.0, 10.0; n=35)	0.015
Wrist extensors	9.0 (8.0, 10.0; n=31)	10.0 (9.00, 10.0; n=35)	0.579
M. quadriceps	10.0 (9.0, 10.0; n=33)	10.0 (9.0, 10.0; n=365	0.778
Ankle dorsiflexors	10.0 (9.0, 10.0; n=33)	10.0 (10.0, 10.0; n=35)	0.222
Neck flexors	8.0 (7.0, 10.0; n=33)	9.0 (7.0, 10.0; n=35)	0.443
M. gluteus medius	8.0 (7.0, 10.0; n=34)	9.0 (6.0, 9.0; n=35)	0.881
M. gluteus maximus	8.0 (6.0, 9.0; n=33)	8.0 (6.0, 9.0; n=35)	0.806
MMT-8 Total Score (x/80)	66.5 (61.0, 77.0; n=34)	72.0 (67.0, 76.0; n=35)	0.134
FI-2: Repetitions (%)			
Shoulder flexion	42.0 (23.0, 60.0; n=31)	38.3 (13.3, 98.3; n=35)	0.967
Shoulder abduction	37.0 (22.0, 62.0; n=31)	46.7 (18.3, 100.0; n=36)	0.549
Head lift	25.0 (12.0, 33.0; n=31)	20.0 (8.3, 41.7; n=35)	0.856
Hip flexion	32.0 (17.0, 50.0; n=31)	21.7 (8.3, 41.7; n=35)	0.117
Step test	43.5 (11.5, 81.5; n=30)	20.0 (6.3, 64.1; n=34)	0.243
Heel lift	27.0 (17.0, 52.0; n=31)	39.6 (25.6, 64.6; n=34)	0.081
Toe lift	23.0 (6.5, 36.0; n=29)	31.3 (15.0, 51.0; n=34)	0.097
FI-2: Muscle exertion Borg CR10 [1]			
Shoulder flexion	4.5 (4.0, 5.8; n=28)	5.0 (2.5, 7.0; n=33)	-
Shoulder abduction	5.0 (4.0, 5.5; n=29)	4.5 (1.5, 7.0; n=33)	-
Head lift	5.0 (4.0, 6.8; n=28)	5.0 (4.0, 7.0; n=32)	-
Hip flexion	4.3 (3.0, 5.0; n=30)	5.0 (4.0, 7.0; n=34)	-
Step test	4.0 (2.0. 5.0; n=26)	4.4 (2.0, 7.0; n=32)	-
Heel lift	4.0 (3.0, 5.0; n=28)	4.0 (3.0, 5.5; n=33)	-
Toe lift	4.0 (2.0, 6.0; n=24)	5.0 (3.0, 7.0; n=33)	-

For nominal variables, the absolute and relative frequencies are shown: n/total valid cases (%).
Continuous variables are described as median and 1st, 3rd quartiles (Q1, Q3).
Data for some clinical parameters were available for fewer patients than the total number of patients in the respective group.
MMT-8: manual muscle testing; FI-2: functional index-2.

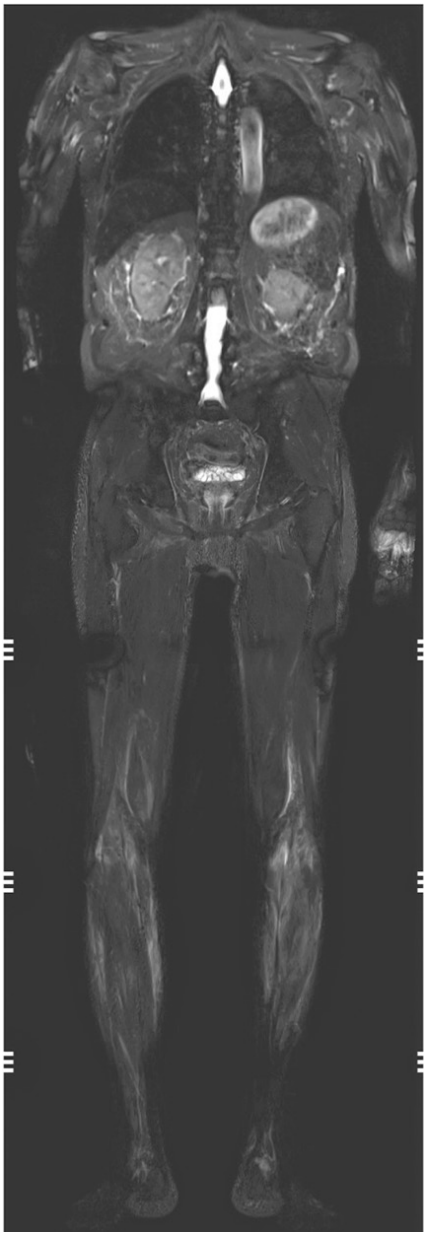

Fig. 1. Whole body MRI of a male patient with SSc-myopathy.
Bilateral presence of myositis M. deltoideus, M. triceps brachii, hand musculature, M. quadriceps (left > right), calf musculature (in particular extensor muscles).

motivation, and difference in stature relative to the tester (34). Our preliminary results raise doubts regarding the suitability of the MMT-8 as an appropriate tool for diagnosis and follow-up in SSc-myopathy patients.

The FI-2 is a validated and reliable outcome measure of impairment of muscle endurance for patients with poly- and dermatomyositis exhibiting neither floor nor ceiling effects (15). In our cohort, this test revealed a major impairment of muscle endurance in myopathy as well as in myositis patients. Having in mind the mild muscle weakness detected by the MMT-8, we deduce that muscle endurance decreases before muscle strength does. Interestingly, different muscle groups seemed be involved in the SSc-myopathy and the myositis group. Especially the distal musculature of the legs and the neck musculature seemed to be affected in SSc-associated myopathy while the thigh and the hip muscles as well as the neck musculature seem to be primarily affected in patients with primary myositis. However, as different factors such as joint contractures, joint synovitis and skin thickening are also likely to affect the performance of SSc-myopathy patients, it remains unclear, to what extent SSc-myopathy patients performed worse due to muscle affection and to what extent their performance was limited because of other disease symptoms. Moreover, a limitation of muscle endurance of the SSc-myopathy and the myositis cohort due to respiratory and cardiac impairment as well as deconditioning in the context of chronic disease cannot be excluded. In an attempt to simplify the time-consuming FI-2, the exam has been cut down to 5 tasks inventing the FI-3, which has been described as an efficient and valid method for assessment of muscle endurance in patients with dermato- and polymyositis (35).

As already described above, 6 of the 16 patients of the SSc-myopathy cohort, who had undergone MRI, showed signs of muscle affection in the MRI. Interestingly, the shoulder girdle as well as the musculature of the proximal legs were the predominant location of muscle affection detected in the MRI. However, the distal musculature including

the musculature of the distal legs and of the hands was affected as well in two patients. The predominant affection of the proximal leg musculature in the MRI is in contrast with the results of the FI-2 of the SSc-patients, in which the performance of distal leg musculature was particularly affected. A possible explanation for this discrepancy could be the presence of joint synovitis, joint contractures and skin thickening in SSc-myopathy patients contributing to a bad muscle performance. Given that these findings are based on a limited number of patients, the results of these analyses should be treated with caution.

Presently, only few studies about musculoskeletal involvement in patients with SSc are available. Boutry *et al*. examined MRI findings of SSc patients with musculoskeletal involvement and illustrated cases with abnormalities of the thigh musculature as well as inflammatory synovitis of the wrist and acroosteolysis of the distal phalanx (36). Compatible with the MRI findings in our cohort, Schanz *et al*. found that 8/18 SSc patients showed the most severe muscle affection seen in MRI scans in the lower legs (37). These data suggest that for this disease entity, whole-body MRI may be more accurate to capture muscle involvement instead of the common practice of performing only MRI of the thighs.

An alternative test used to assess muscle weakness and function is hand-held dynamometry (HHD). HHD measures the peak isometric force generated from a single muscle group and has been proven to have good to excellent intra- and inter-rater reliability (16). According to Baschung *et al*., this test can be recommended to evaluate isometric muscle strength of single muscle groups in patients with myositis, whereas the MMT-8 should not be used to evaluate changes in single muscle groups due to its insensitivity (16). HHD has also been used in SSc, examining knee extension and / or handgrip strength and linking it with the degree of functional disability (31, 38). Handgrip and knee extension strength assessed by HHD have been shown to be remarkably impaired in SSc patients with sarcopenia compared to SSc patients without sarcopenia (38). On the other hand, Pettersson *et al*. assessed muscle strength of the lower extremities in SSc patients by the timed-stands test, which measures the time needed to complete 10 full stands from a sitting position on a 46 cm high chair without using the arms (39). In his analysis, SSc patients showed a reduced muscle strength of the lower extremities. However, a disadvantage of this test is that it evaluates only the muscle strength of the proximal lower extremity.

Our retrospective study showed that the assessment of muscle involvement in SSc by functional tests established for primary myositis has limitations. Given the multi-organ disease character, confounders such as skin, joint, cardiovascular involvement should be taken into account when performing functional tests. Furthermore, the results of the FI-2 and the whole body-MRI suggest that different muscle groups can be affected in SSc-myopathy and primary myositis patients. Whole body-MRI might therefore be superior to assessing only the thighs, as commonly practiced when screening for primary myositis, to accurately capture the disease extent of patients with SSc-myopathy. CK elevation might be a supporting factor in establishing the diagnosis, however, potentially due to lower body mass and lower physical activity or differences in disease pathology, CK levels in our subjects were in the lower range. Therefore, low or normal CK levels might not necessarily exclude an underlying myopathy in SSc. The improvement of overall disease activity, muscle-related features and cardiac manifestations at one-year follow-up might point towards a benefit of immunosuppressive and physical therapy. In comparison to previous studies, anti-centromere-positivity occurred in patients with SSc-myopathy although, interestingly, vascular complications were much more prevalent in the non-myopathy cohort.

Given the heterogeneity of patients with SSc-myopathy, larger cohorts such as the EUSTAR-SCTC cohort will be able to provide answers that are more conclusive and to drive the process of consensus diagnostic criteria.

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