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Journal

Journal of Scleroderma and Related Disorders, 3(3)

ISSN

2397-1983

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Publication Date

2018-10-01

DOI

10.1177/2397198318774301

Peer reviewed

Original Research Article

JSRD | Journal of Scleroderma and Related Disorders

Journal of Scleroderma and Related Disorders
2018, Vol. 3(3) 228–236

DOI: 10.1177/2397198318774301
journals.sagepub.com/home/jso
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Validation of Sonography findings of synovitis and tenosynovitis of hands and wrists in patients with systemic sclerosis

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Abstract

Objectives: Validating musculoskeletal ultrasound features of the joints and tendons of the hands in a large scleroderma cohort.

Methods: A total of 81 scleroderma patients participated in this prospective, cross-sectional study. Grayscale and power Doppler musculoskeletal ultrasound images of 13 joints and 5 tendons of the wrist and hand were obtained. Clinical assessment included modified Rodnan skin thickness score, joint count, and Scleroderma Health Assessment Questionnaire. Face validity, content validity, construct validity, and feasibility were assessed.

Results: Mean age was 53.8 years (range 22–80), 76.5% were females, and disease duration ranged from 0.25 to 29 years. Mean length of the examination was 36 min. Scleroderma Health Assessment Questionnaire–Disability Index correlated with musculoskeletal ultrasound erosions ($r = 0.5$, $p = 0.0003$). Skin score correlated with tendinitis grayscale ($r = 0.26$, $p = 0.02$). Intra-reader correlation coefficient for musculoskeletal ultrasound was 0.96 for the joints and could not be calculated for tendons because there were too few positive findings. When tendon changes existed, percent of agreement was 77.7%–83.3%.

Conclusion: Musculoskeletal ultrasound of 13 joints and 5 tendons of the hands and wrist has face and content validity. Construct validity was shown for the tendons and erosion scores. Feasibility and reliability were partially validated.

Keywords

Ultrasound, scleroderma, hands, validation

Date received: 28 November 2017; accepted: 4 April 2018

Introduction

The use of musculoskeletal ultrasound (MSUS) in rheumatology is rapidly growing and is increasingly used in systemic sclerosis (SSc). To date, scoring methods as well as selection of joints and tendons varies among studies.[1–3] A uniformly accepted and validated method for ultrasound of the joints and tendons in SSc will provide a pathway to prove successful therapies of the joints/tendons in SSc. Thus, we have sought to validate several aspects of MSUS according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) filter.

According to the OMERACT filter, truth is the measure of truthful, unbiased, and relevant results. The word captures issues of face, content, construct, and criterion validity. Discrimination captures issues of reliability and sensitivity

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Table 1. Inclusion and exclusion criteria.

Inclusion criteria
1. Age ≥ 18.
2. SSc by ACR criteria.
3. Patients understand information in the informed consent and comply with the study requirements.
Exclusion criteria
1. Patients with vasculitis, sarcoidosis, overlap of scleroderma and lupus, inflammatory myopathies, or other ACR-defined connective tissue disease.
2. SSc sine sclerosis.
3. Previous arthroplasty, synovectomy, or fusion of the MCP, PIP, or wrist joints.
4. Severe major organ involvement or a life-threatening disease (cancer, infection).
5. Patients whose concomitant diseases may interfere with the ability to appropriately evaluate outcomes. Examples are
a. Uncontrolled diabetes, hypothyroidism, or other metabolic disorders,
b. Crystal disease,
c. Severe, uncontrolled local or generalized OA.
6. Intra-articular steroid injection of any joint within 1 month excluded that joint.

ACR: American College of Rheumatology; SSc: systemic sclerosis; OA: osteoarthritis; MCP: metacarpophalangeal; PIP: proximal interphalangeal.

to change (the OMERACT filter 2.0).[4] Our primary aims were to examine the feasibility, face, content, and construct validity as well as reliability for a semiquantitative MSUS scoring system for joints and tendons of the hand and wrist in SSc. Our secondary aim was to corroborate the prevalence and distribution of synovitis and tendinitis in the hand and wrists in SSc patients.

Materials and methods

Participants were consecutive SSc patients, defined by 1980 American College of Rheumatology (ACR) Scleroderma Criteria, who visited the rheumatology outpatient clinic at the University of California, Los Angeles (UCLA) between January and July 2013, regardless of clinical symptoms or signs of arthritis. Inclusion and exclusion criteria are described in Table 1.

The study was approved by the local ethics committee and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Clinical assessment

After screening (Table 1), patients underwent clinical assessments on the same day as the MSUS examination. In total, 28 tender and swollen joint count,[5] modified Rodnan skin thickness score (mRSS),[6] and small joint contracture assessments were done by an experienced rheumatologist. Assessments were performed of the dominant hand in as close as possible to the neutral position (metacarpophalangeal (MCP) joints 2–5, proximal interphalangeal (PIP) joints 2–5, distal interphalangeal (DIP) joints 2–5, and wrist) using a goniometer.[7] Flexion deformity of more than 100 degrees was considered as severe contracture. Scleroderma Health Assessment Questionnaire (SHAQ), a patient self-administered instrument that focuses on activities of daily living, which includes the Health Assessment Questionnaire–Disability Index (HAQ-DI) plus five 100-mm visual analog scales (VASs) was completed by the patients. Each VAS asked, "In the last week, how much have your symptoms—Raynaud's phenomenon, digital ulcerations, gastrointestinal and lung symptoms and overall scleroderma interfered with your activity?").[8–11] The physicians and patients evaluated global assessment of overall disease activity on a 100-mm VAS scale.

Demographic and clinical data (age, disease duration, and gender) and lab (hemoglobin in the recent year), echocardiogram, high-resolution computed tomography (HRCT), and right heart catheterization (RHC) results were abstracted from medical charts. Lung involvement was defined by fibrosis, reticulation, ground glass, and/or honeycombing findings on HRCT. Patients who did not have HRCT results in their charts were considered to be without lung involvement if they were clinically asymptomatic, and both the pulmonary function tests (forced vital capacity (FVC), diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for hemoglobin) were normal and the SHAQ for breathing was also zero. Pulmonary hypertension (PH) was defined as resting right ventricle systolic pressure ≥ 40 mmHg by echocardiogram[12] or RHC resting mean pulmonary arterial pressure ≥ 25 mmHg with pulmonary capillary wedge pressure (CWI) ≤ 16 (RHC).

Sonographic assessment

One investigator (A.S.-E.) performed all the MSUS examinations. The MSUS investigator had 1-year experience in MSUS and was trained prior to the study by an experienced MSUS investigator (A.B.-A., 5 years of MSUS experience, performed more than 2500 scans) over 30 supervised MSUS examinations of hands for acquisition and over 150 scans for scoring of the images.

The clinicians (D.E.F., P.C., S.K.) and the MSUS investigator were blinded to each other's findings. MSUS scanning methods were performed according to published guidelines:[13] grayscale (GS) and power Doppler (PD) MSUS exams were performed with a General Electric Logic E9 scanner by means of a 5–16 MHz linear array transducer. B-mode frequency was 15 MHz. PD settings were: pulse repetition frequency 800 Hz, frequency 10 and low wall filter.Receiver gain settings were controlled to eliminate artifacts.

Evaluation of joints. MSUS exam of 13 joints (wrist, MCPs 2–5, PIPs 2–5, DIPs 2–5) was performed of the dominant hand. Long- and short-axis images were obtained. The transducer was positioned on the midline of the joint in longitudinal view with the joints in 0-degree position. Patients with contractures were examined as much as the degree of contractures allowed. The environment was optimized for gel temperature, lighting, and temperature of the room.

Evaluation of tendons. Long- and short-axis images were taken. The transducer was positioned on the midline of the tendon examined in the longitudinal plain. On the transverse plane, the transducer scanned proximally and distally. Tendons included in this analysis were extensor carpi radialis brevis and longus (compartment 2), extensor digitorum communis and extensor indicis proprius (compartment 4), extensor carpi ulnaris (compartment 6), and flexor tendons at the MCP 3 and 4 levels.

Scoring methodology. One investigator (A.S.-E.) scored the MSUS examinations. Images were saved and read at the end of the study. In case of uncertainty for all aspects of the MSUS, a consultation with another MSUS expert was done (A.B.-A.) and consensus was reached. Synovitis was defined according to the published OMERACT definitions.[14] For joint scoring, GS 4-grade semiquantitative scale (range 0–3) was used combining both synovitis and effusion together according to Scheel et al.[15] and PD semiquantitative scale (range 0–3) was used according to Skudlarek et al.[16] Tenosynovitis (tendons with synovial sheath) was scored according to Naredo et al.[17] and Bruyn et al.[18] by GS (range 0–3) and PD (range 0–3).

GS and PD scores for joints were calculated by summing up scores for all examined views (maximum 28 views: dorsal, radial, ulnar, and palmar wrist as well as the dorsal and volar long and short aspects of MCPs 2–5, PIPs 2–5, and DIPs 2–5) and dividing by the sum of views that were examined. This "averaging" was done to overcome the underestimation bias in the patients who had contractures preventing accurate MSUS and therefore had fewer joints evaluated. GS and PD scores for tendons were calculated by dividing the total sum of scores for all examined views on the tendons (maximum five views: compartments 2, 4, 6, flexors of MCPs 3 and 4) by the number of tendon views that were examined. This method compensated for unmeasurable tendons.

Bone erosions were present or absent on the radial aspect of MCP 2 and on the ulnar aspect of MCP 5 as well as on the other 28 positions examined. Presence of either a defect in the surface of the bone seen in two planes or a bone defect creating extensive bone destruction (Skudlarek score grade 2 or 3, respectively)[16] was defined as an erosion.

Statistical analysis

Descriptive analysis for demographic and visceral involvements used means and standard deviations for normally distributed continuous variables and percentage for dichotomous variables. Validation was assessed using the OMERACT filter.[19] Spearman's correlation coefficient was used to test convergent construct validity by correlations with tender joint count (TJC), swollen joint count (SJC), VAS pain, mRSS, and HAQ-DI. Correlation between hemoglobin and MSUS scores was examined for construct discriminant validity.

Range of patients with various ages, disease duration, functional abilities, visceral involvement, both genders, presence of small joint contractures, and limited and diffuse disease was described for content validity. Face validity was examined through a literature search for credibility of the measure. Feasibility was sought by examining the time to conduct the measurements. Construct validity was evaluated by the assessment of the relationship between MSUS scores (synovitis, tendinitis, and erosions) and clinical parameters (TJC, SJC, pain, mRSS, HAQ-DI) by the determination of Pearson correlation coefficients (r_s). Intraobserver reliability was assessed by re-examination of five patients within 2 weeks by the same investigator, using the intra-class correlation coefficient (ICC). The 95% confidence interval was generated corresponding to the p values from the F test. Statistical analysis was performed with the software R3.0, "psych" version 1.4.4 (http://CRAN.R-project.org/package=psych) and "Hmisc" version 3.14-4 (http://CRAN.R-project.org/package=Hmisc).

Results

Patients

In total, 85 SSc patients were enrolled in the study and examined. Four patients were excluded after chart review demonstrating evidence of overlapping arthritic conditions (crystal disease, psoriasis, sarcoidosis, dermatomyositis). Thus, 81 patients completed the MSUS exam (Figures 1 and 2). Mean age of the SSc patients was 53.8 years and 76.54% were females. Mean disease duration was 7.43 years (range, 0.25–29). Other clinical data are given in Tables 2 and 3.

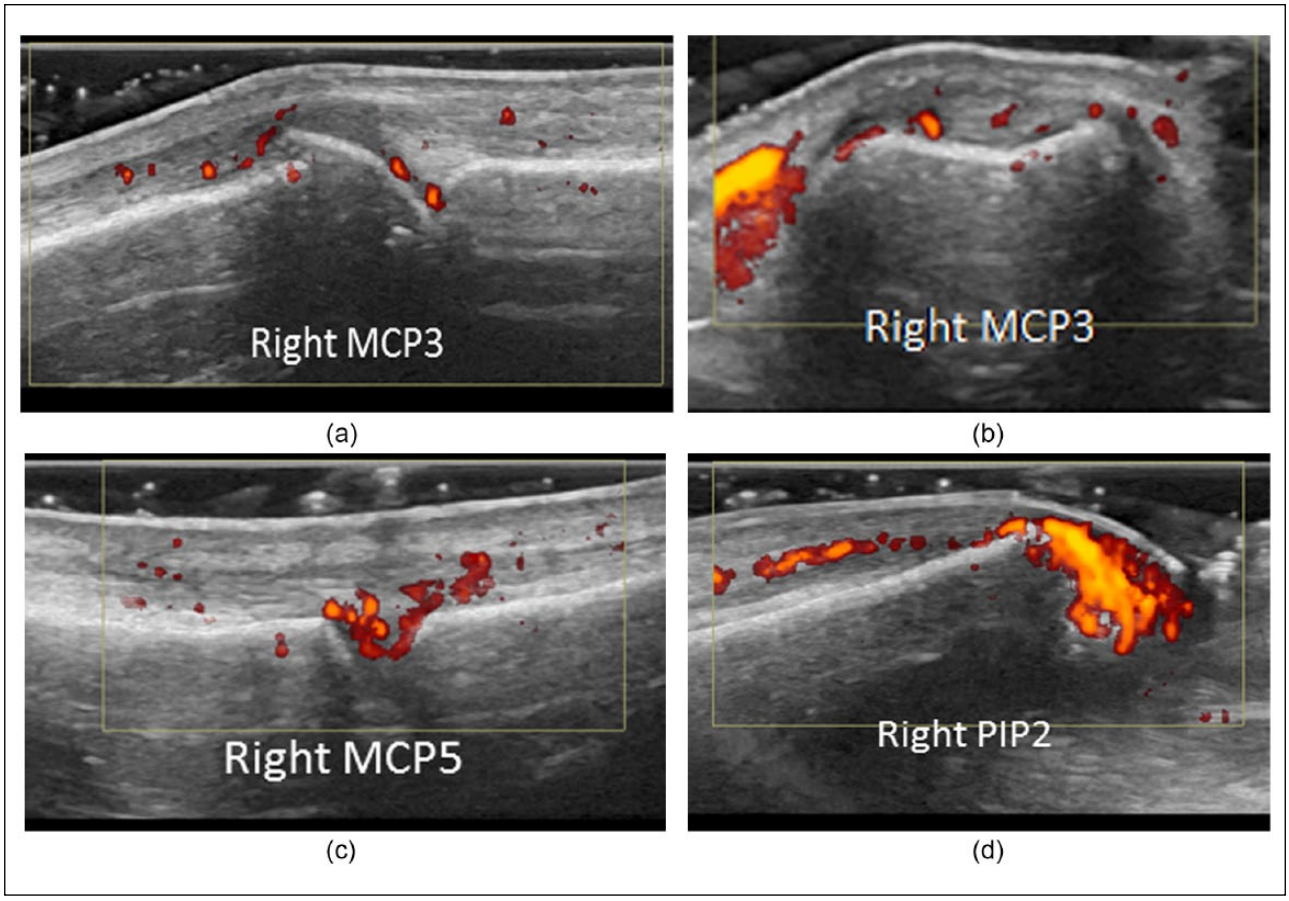

Figure 1. This is a 54 years old female with diffuse scleroderma with pulmonary and cardiac involvement as well as arthritis. She was diagnosed 7 years prior to her enrolment. On physical examination, she had an active disease with arthritis and skin score of 12. The patient had a 25 degree flexure contracture on the third MCP which is shown on the longitudinal image (Image 1A) as misalignment of the metacarpal bone proximal to the MCP joint. The patient also had 115 degrees flexure contracture on the right second PIP. Images 1A (longitudinal) and 1B (cross sectional) show synovitis on the right third MCP joint. Image 1C shows synovitis as well as tendonitis on the fifth MCP. Despite the severe contracture on the second PIP (Image 1D), PD signal along the tendon is noted.

Ultrasound features

A total of 2097 views were taken of joints. Most views (92.4%) did not show PD signal (PD 0). Only 4.6% of the views showed PD + 1 and 1.4% showed PD + 2. Only three patients had PD + 3 scores and in all of them it was observed in only one joint. As shown in Table 4, unlike rheumatoid arthritis (RA), the prevalence of synovitis was rather similar at the wrist, MCP, PIP, and DIP levels. Description of the OMERACT filter for validation of measures based on Clements et al.[6] and the evidence found in our study is summarized in Table 5.

Face validity. Elhai et al.[1] and Cuomo et al.[3] support the face validity of MSUS assessments of joints and tendons (PD and GS) of the hands and wrists in SSc patients, including 97 patients and describing the changes found.

Content validity. Our patients were of both genders and encompassed a wide range of age, disease duration, scleroderma subtypes, and visceral involvement (Tables 2, 3, and 6). Two patients had previous scleroderma renal crisis, three had previous lung transplantation, and one had previous kidney transplantation.

In total, 80 patients had positive GS signals and 47 patients had positive PD signals in at least one joint, while only 43 and 53 patients had positive PD and GS signals, respectively, in at least one tendon. When only those patients with positive MSUS findings in the joints or tendons were examined, their ranges of age, disease duration, gender, mRSS, lung involvement, and disease types were similar to those of the total group, thus supporting the content validity of MSUS (Table 3).

Contractures. Nine patients had flexion deformity of over 100 degrees in at least two joints. These severe contractures precluded the examination of the PIPs as well as the volar

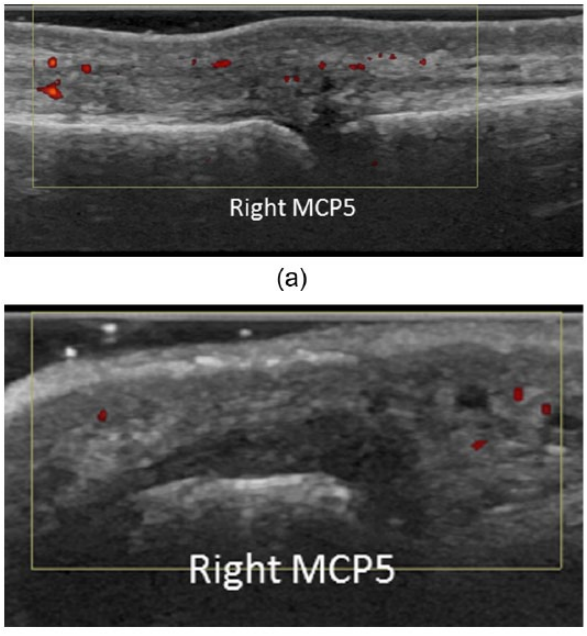

Figure 2. This is an MSUS of the right fifth MCP of a 27-year-old male patient who was diagnosed several months prior to the examination with diffuse scleroderma with skin, lung, and GI involvement. He had an active disease with digital pitting scars and a skin score of 14. The transducer is placed over the right fifth metacarpophalangeal joint in a longitudinal position (a) showing tendonitis. There are positive PD signals over the extensor tendon as well as hypoechoic signal around the tendon. On the cross-sectional view (b), there is a positive PD signal over the tendon.

aspect of the MCPs and DIPs in these patients. A total of 10 patients had a flexion deformity of 45–95 degrees in at least two PIPs. This was adjusted for in the analyses as noted above. And 10 patients had no contractures of the PIP joint. The rest of the patients had mild flexion contractures.

Construct validity. Convergent construct validity demonstrated strong positive correlations between the HAQ-DI part of the SHAQ and erosions by MSUS ($r=0.5$, $p=0.0003$, Spearman) and a weak positive correlation between skin score and tendinitis (Table 7). No correlations were found between the joint score and other clinical parameters.

Construct discriminant validity showed, as would be predicted, no correlation between hemoglobin and MSUS scores (joint GS: $p=0.5$, $r=0.08$; PD joint: $p=0.14$, $r=-0.19$; tendon GS: $p=0.47$, $r=0.09$; tendon PD: $p=0.83$, $r=0.02$).

Feasibility. The mean time for US examination was 36 min (range18–66) for the one MSUS investigator in whom it was tested. No specific examination of various ultrasound machines and costs was undertaken.

Reliability. There were a large number of joints, the GS and PD scores of which were zero. Thus, only PD or GS reading with 1–3+ were included in the ICC calculation, albeit only accounting for 7.6% of all views. Intra-reader ICC for joints was calculated in fivefivepatients with 96 joints (volar and dorsal aspects were scored separately, and thus each patient had a maximum of 28 scores, unless contractures precluded some joints from being examined). ICC for joint GS was 0.96 with 95% confidence interval (CI) of 0.64–0.98 and that for joint PD was 0.97 with 95% CI of 0.64–0.98. There were too few positive tendon scores to reliably calculate ICC. For the few positive tendon scores, agreement was 77.7% for GS and 83.3% for PD ($N=18$).

Inter-observer reliability was as follows: for PD, ICC—0.61, kappa—0.69, and weighted kappa—0.65 (good agreement) and, for GS, ICC—0.54, kappa—0.48, and weighted kappa—0.51 (moderate agreement).

Discussion

Clinical evaluation of digital ulcers and systemic sclerosis is difficult and challenging and the use of ultrasound may improve those evaluations.[20] This MSUS study examined 81 SSc patients, the largest cohort of SSc patients subjected to systematic MSUS testing to our knowledge. We applied a semiquantitative score in B-mode and PD to assess 13 joints and 5 tendon compartments of hands and wrists.

This is the first study to provide a comprehensive analysis of several aspects of the validity of MSUS examination of the hands and wrists in SSc patients. Similar to a previous study,[1] we showed that most joints either did not show PD signals at all or showed only low grade PD signals.

Face validity reflects the logic of the method and findings. Two other articles support the face validity of MSUS assessment of joints and tendons (PD and GS) of the hands and wrists in SSc patients. Cuomo et al.[3] assessed MSUS of wrist, MCPs, PIPs, and DIPs (15 joints) in 45 SSc patients and found joint effusion (49%), marginal bone erosions (11%), and periarticular calcinosis (27%). Elhai et al.[1] used a semiquantitative PD scoring system to evaluate joints (wrist, MCPs, PIPs, and DIPs of each hand) and a qualitative method to assess tendons in 52 SSc patients. They found 46% synovitis and 27% tenosynovitis.

Content validity was demonstrated by including a wide range of patients (Tables 2 and 3), even if one considers only the MSUS-positive groups, as outlined in our results. Construct convergent validity for the five tendons' scores was demonstrated by showing the correlation between skin score (mRSS) and tendinitis by GS, although its strength is limited by the relatively low degree of correlation. Convergent validity was also shown for erosions where the 13 MSUS joints' erosion scores correlated with the HAQ-DI. The association between HAQ-DI and ultrasound erosions is of importance, since in RA patients the association between HAQ and erosions by both X-rays and magnetic resonance imaging (MRI) was found.[21,22]

Table 2. Clinical features of all patients.

	Mean	Range	N
Age (years)	53.8	22–80	81
Females (%)	76.54	NA	81
Mean disease duration (years)	7.43	0.25–29	81
Limited disease (%)	25.92	NA	81
Right handedness	76	NA	81
ESR[a] (mm/h)	19	1–58	31
Hemoglobin (g/dL)	12.43	8.5–16.1	61
Telangiectasia	30	NA	46
Active digital ulcers	42	NA	81
Pitting scars	14	NA	31
mRSS[b]	9.33	0–32	71
Sclerodactyly[c]	55	NA	74
Severe contractures	9	NA	81
At least one swollen joint	22	NA	67
At least one tender joint	27	NA	68
Definite or possible lung involvement[d] (%)	83.56	NA	70
PH[e]	7	NA	64
Immunosuppressive therapy[f]	12	NA	81

NA: not applicable; ESR: erythrocyte sedimentation rate; mRSS: modified Rodnan skin score; PH: pulmonary hypertension.
N = number of patients, unless stated differently.
[a]Only four patients had ESR greater than 40.
[b]Skin score was measured on the same day of the first MSUS exam.
[c]Sclerodactyly on the examined hand was defined as a Rodnan score of at least 1 point on the fingers.
[d]In total, 47 patients had definite lung involvement and 8 had possible lung involvement. We could not obtain the results of HRCT in 11 patients, of which 2 were considered with no lung involvement (HAQ breathing 0, normal PFT) and 6 were considered as having possible lung involvement (abnormal PFT).
[e]PH was defined either by echo (RVSP≥40) or by RHC (PAP≥25, CWP<16).
[f]Five patients were treated with tocilizumab, four were on rituximab, two were treated with cyclophosphamide, and one patient was on rituximab and cyclophosphamide.

Table 3. Clinical data for patients with positive MSUS findings.

	PD + joints	GS + joints	GS + tendons	PD + tendons
Age, years (range)	53.19 (22–73)	53.77 (22–73)	54.7 (22–73)	53.56 (22–73)
Females, %	80.2	81.25	82.71	83.95
Mean disease duration, years (range)	7.77 (0.25–29)	7.48 (0.25–29	06.92 (0.41–29)	7.2 (0.83–16)
Limited disease, % (N)	27.65 (47)	26.25 (80)	22.64 (53)	23.33 (30)
Hemoglobin, g/dL (range)	12.13 (8.5–16.1)	12.42 (8.5–16.1)	12.54 (8.8–16.1)	12.65 (8.8–16.1)
mRSS (range)	9.38 (0–32)	9.05 (0–32)	10.17 (0–28)	10.36 (0–32)
Lung disease, % (N)*	80.95 (42)	83.33 (73)	79.16 (48)	78.58 (28)

MSUS: musculoskeletal ultrasound; PD: power Doppler; GS: grayscale; mRSS: modified Rodnan skin score.
The table shows the ranges of age, disease duration, and other clinical data only for patients with positive MSUS findings in the joints or tendons. When only those patients were examined, their ranges of the above parameters were similar to those of the total group.
*All p values were > 0.05.

Interestingly, we did not find correlations between MSUS and TJC, SJC, pain, and HAQ-DI. Similarly, Weise et al.[23] did not find high correlations between skin measures and musculoskeletal measures among RA patients. Damjanov et al.[24] found only weak to moderate correlations of US disease activity score (DAS) with Health Assessment Questionnaire–Disability Index (HAQ-DI; Pearson correlation coefficient = 0.28, p = 0.008). The lack of correlation between TJC, SJC, pain, and MSUS synovitis is in contrast to our expectations. Nevertheless, it is possible that low-grade MSUS synovitis, as it was found in our study, may not be discerned clinically. This was supported by several studies that have examined joints and tendons in SSc using MSUS.[1–3] For example, Elhai et al. found that synovitis and tenosynovitis were more frequently detected with US in SSc patients (46% and 27%, respectively) than with clinical examination (15% and 6%, respectively). Cuomo et al.[3] found that in SSc patients the

prevalence of synovitis as detected by US was significantly higher than that found by clinical examination (26 vs 15 out of 45 cases; p = 0.03). Importantly, Gordon et al.[25] examined TJC and SJC versus MSUS showing a very poor positive predictive value of about 5% for swelling.

We used a 5-compartment tendinitis score that included compartments 2, 4, and 6 of the wrist extensors and flexors of MCPs 3 and 4 according to Naredo et al.[17] who used in RA a 7-compartment score that included all the above as well as peroneus longus and brevis and tibialis posterior. We also examined compartment 1 at the wrist which Naredo et al.[17] did not include due to the proximity to the radial artery that could produce Doppler artifacts. We included as well wrist flexors that were excluded by Naredo et al.[17] since it was suggested previously that the frequent variability may interfere with the ability to score properly. Nevertheless, sensitivity analysis showed that adding compartment 1 and wrist flexors did not affect the results (paired t-test: p = 0.13 for GS, p = 0.1 for PD).

Table 4. Percent of PD signals across the different hand joints.

	Wrist	MCPs	PIPs	DIPs	All hands
PD 0 (%)	95	92.4	95.9	93.4	92.4
PD 1 (%)	2.4	6.2	3.2	5.4	4.6
PD 2 (%)	1.8	1.5	0.7	1.3	1.4
PD 3 (%)	0.6	0.31	0	0	0.19

PD: power Doppler; MCPs: metacarpophalangeal joints; PIPs: proximal interphalangeal joints; DIPs: distal interphalangeal joints.
The table shows the distribution of power Doppler signals across different joints.

Limitations

Our study has some limitations. ICCs for the five tendon scores could not be adequately calculated due to too few positive findings. This, however, may be characteristic of SSc hand arthritis. Nevertheless, percent of agreement for the tendons score was 77.7% for GS and 83.3% for PD.

We did not examine other joints than the hand and wrist, as the hands/wrists are the most frequently examined small joints when using the MSUS. To increase feasibility, we chose to evaluate only one hand (the dominant hand) and we did not include either the first finger or the feet in the evaluation. This was reasonable as SSc pathology can be found more frequently in the hands rather than the feet.[26]

On the other hand, we included the DIPs as the distal phalanges are often involved in SSc patients.

For the examination of the tendons in compartment 2 of the wrist extensors, only 70% of patients were examined. We found no differences between the scores for the 70% who did and the 30% who did not have compartment 2 measured (Welch's two-sample t-test: p = 0.22 for GS, p = 0.95 for PD; data not shown). We had pulmonary function test and HAQ breathing results for all patients and HRCT results of the lungs were available in 86% of the patients.

Table 5. Evidence for validation of joint and tendons scores using the OMERACT filter.

Filter	Validity character	Score of 13 joints	Erosion score	Score of five tendons	N
Truth—Does it measure what it intends?	Face	Yes	Yes	Yes	NA
	Criterion	ND	ND	ND	NA
	Content	Yes	Yes	Yes	N = 81
	Construct convergent	No	Yes[a] Erosions correlated with HAQ-DI (p = 0.0003, r = 0.5)	Yes Tendinitis (GS) correlated with skin score (see Table 6)	N = 71 (skin score) N = 64 (SJC)
	Construct discriminant	Yes Hemoglobin did not correlate with US scores	Yes Hemoglobin did not correlate with US scores	Yes Hemoglobin did not correlate with US scores	N = 45
Discrimination between situation of interest	Reliability	Yes ICC: 0.96 (GS) ICC: 0.97 (PD)		ND[b]	N = 5
Feasibility	Feasibility	Yes Mean length of examination was 36 min		Yes Mean length of examination was 36 min	N = 81

OMERACT: Outcome Measures in Rheumatology Clinical Trials; NA: not applicable; ND: not done; ICC: intra-class correlation coefficient; PD: power Doppler; GS: grayscale; HAQ-DI: Health Assessment Questionnaire–Disability Index.
The table provides evidence for validation of joint and tendon scores using the OMERACT filter.
[a]By Spearman's correlation coefficient.
[b]ICC for tendons could not be calculated due to too few positive findings. Agreement for the tendon score was 77.7% for GS and 83.3% for PD.

Table 6. Mean MSUS scores across different age groups in scleroderma patients.

Age (years)	N	Joint GS[a]	Joint PD[a]	Tendinitis GS[a]	Tendinitis PD[a]
20–29	5	0.3 (0.03–0.46)	0.05 (0–0.25)	0.23 (0–0.71)	0.12 (0–0.29)
30–39	8	0.27 (0.03–0.53)	0.14 (0–0.47)	0.29 (0–0.67)	0.06 (0–0.29)
40–49	20	0.43 (0.06–1.33)	0.08 (0–0.88)	0.41 (0–1.29)	0.3 (0–1.2)
50–59	16	0.54 (0.14–1.5)	0.19 (0–1.6)	0.32 (0–1.62)	0.24 (0–1.75)
60–69	24	0.46 (0–1.17)	0.06 (0–0.33)	0.36 (0–1.6)	0.3 (0–2.4)
70–79	7	0.29 (0.07–0.5)	0.03 (0–0.12)	0.26 (0–0.86)	0.2 (0–0.57)
80–89	1	0.67	0	0	0

MSUS: musculoskeletal ultrasound; PD: power Doppler; GS: grayscale.
The table shows the mean MSUS scores across different age groups in scleroderma patients.
[a]Mean (range).

Table 7. Correlation between MSUS tendinitis scores and clinical findings.

	Tendons GS, r(p)	Tendons PD, r(p)	N
MRSS	0.23 (0.04)	0.11 (0.34)	70
HAQ-DI	0.19 (0.19)	0.04 (0.78)	45
Pain	−0.03 (0.74)	0.05 (0.61)	73
TJC	−0.03 (0.79)	0.07 (0.58)	63
SJC	−0.03 (0.76)	0.007 (0.95)	63

MSUS: musculoskeletal ultrasound; GS: grayscale; PD: power Doppler; mRSS: modified Rodnan skin score, HAQ-DI: Health Assessment Questionnaire–Disability Index; TJC: tender joint count; SJC: swollen joint count.
The table shows the Pearson correlation coefficients and p values for the relationship between MSUS tendinitis scores and clinical findings.

Some of our patients had severe hand contractures, preventing full evaluation of all joints but this is inherent in the disease and cannot be avoided.[27]

We could not obtain X-ray results for most patients in order to assess erosions. Wakefield et al.[28] have found that in early RA patients sonography detected 6.5-fold more erosions than did radiography, in 7.5-fold the number of patients. In late-stage disease, these differences were 3.4-fold and 2.7-fold, respectively. Further study is needed in order to compare conventional radiography and US for detecting erosions in scleroderma.

Our principle goal in this study was to examine the validity of ultrasound for use in the musculoskeletal manifestations of SSc. The use of background medications did not impinge on this aspect of the study. We realize that the use of disease-modifying antirheumatic drugs (DMARDs) and corticosteroids could impact the frequency of abnormal findings and this is certainly a limitation of the study. It is nevertheless impressive that 98.7% of the SSc patients had positive GS signals on ultrasound despite this limitation. In the future, a longitudinal study with restrictions on background medications and measurement over time is necessary to define discrimination and responsiveness.

Finally, our patients were classified according to the 1980 SSc classification criteria, since this work was done before the 2013 criteria were published.

Conclusion

In our cross-sectional study, we validated a majority of the criteria necessary to fully validate MSUS of the joints/tendons of the hands and wrists in SSc patients. MSUS of the hand and wrist for the 13 joint and the 5 tendon scores has feasibility, face validity, content, construct validity, and reliability. Complete validation requires a longitudinal cohort to validate responsiveness and discrimination.

Acknowledgements

We would like to acknowledge Mrs Emma Hasan who provided and cared for study patients. We have full control of all primary data and we agree to allow the journal to review our data if requested. A.S.-E., D.E.F., V.K.R., and A.B.-A. contributed to the planning of the study. P.C., S.K., D.E.F., A.S.-E., and A.B.-A. contributed to the conduct of the study. A.S.-E., T.W., P.C., V.K.R., T.W., D.E., L.D., and D.E.F. contributed to the writing, editing, and reporting of the work described. L.D. and D.E. contributed to the statistical analysis.

Declaration of conflicting interests

A.S.-E., A.B.-A., L.D., S.K., N.H.B., T.W., D.E., and P.C. declare that they have no conflicts of interest. V.K.R. reports support from Genentech, Bristol Meyer Squibb, Pfizer, and Amgen. D.E.F. reports grant/research support from AbbVie, Actelion Pharmaceuticals US, Amgen, BMS, Cytori, GSK, NIH, Novartis Pharmaceutical Corporation, Pfizer Inc., Roche/Genentech, UCB, and Janssen Pharmaceutical Product.

Ethical statement

All human studies have been approved by the ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave their informed consent prior to their inclusion in the study.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Elhai M, Guerini H, Bazeli R, et al. Ultrasonographic hand features in systemic sclerosis and correlates with clinical, biologic, and radiographic findings. *Arthritis Care Res (Hoboken)* 2012; 64(8): 1244–1249.
2. Generini S, Steiner G, Miniati I, et al. Anti-hnRNP and other autoantibodies in systemic sclerosis with joint involvement. *Rheumatology (Oxford)* 2009; 48(8): 920–925.
3. Cuomo G, Zappia M, Abignano G, et al. Ultrasonographic features of the hand and wrist in systemic sclerosis. *Rheumatology (Oxford)* 2009; 48(11): 1414–1417.
4. Boers M, Kirwan JR, Gossec L, et al. How to choose core outcome measurement sets for clinical trials: OMERACT 11 approves filter 2.0. *J Rheumatol* 2014; 41: 1025–1030.
5. Grunke M, Witt MN, Ronneberger M, et al. Use of the 28-joint count yields significantly higher concordance between different examiners than the 66/68-joint count. *J Rheumatol* 2012; 39(7): 1334–1340.
6. 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; 22(7): 1281–1285.
7. Serup J. Measurement of contractures of the digits in systemic sclerosis. Development of digit-goniometers and definitions of normal joint motility of the digits of elderly persons. *Dermatologica* 1983; 167(5): 250–255.
8. Poole JL and 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.
9. Fries JF, Spitz P, Kraines RG, et al. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980; 23(2): 137–145.
10. 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): 255–273.
11. Pope JE, Bellamy N, Seibold JR, et al. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum* 2001; 44(6): 1351–1358.
12. Hsu VM, Chung L, Hummers LK, et al. Development of pulmonary hypertension in a high-risk population with systemic sclerosis in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) cohort study. *Semin Arthritis Rheum* 2014; 44(1): 55–62.
13. Backhaus M, Burmester GR, Gerber T, et al. Working Group for Musculoskeletal Ultrasound in the EULAR Standing Committee on International Clinical Studies including Therapeutic Trials. Guidelines for musculoskeletal ultrasound in rheumatology. *Ann Rheum Dis* 2001; 60(7): 641–649.
14. Wakefield RJ, Balint PV, Szkudlarek M, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32(12): 2485–2487.
15. Scheel AK, Hermann KG, Kahler E, et al. A novel ultrasonographic synovitis scoring system suitable for analyzing finger joint inflammation in rheumatoid arthritis. *Arthritis Rheum* 2005; 52(3): 733–743.
16. Szkudlarek M, Court-Payen M, Jacobsen S, et al. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. *Arthritis Rheum* 2003; 48(4): 955–962.
17. Naredo E, D'Agostino MA, Wakefield RJ, et al. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. *Ann Rheum Dis* 2013; 72(8): 1328–1334.
18. Bruyn GA, Hanova P, Iagnocco A, et al. Ultrasound definition of tendon damage in patients with rheumatoid arthritis. Results of an OMERACT consensus-based ultrasound score focusing on the diagnostic reliability. *Ann Rheum Dis* 2014; 73(11): 1929–1934.
19. Bellamy N. Science of assessment. *Ann Rheum Dis* 2005; 64(Suppl 2): ii42–ii45.
20. Hughes M, Tracy A, Bhushan M, et al. Reliability of digital ulcer definitions as proposed by the UK Scleroderma Study Group: a challenge for clinical trial design. *Journal of Scleroderma and Related Disease* 2018; 3(2): 170–174.
21. Gherghe AM, Ramiro S, Landewé R, et al. Association of the different types of radiographic damage with physical function in patients with rheumatoid arthritis: analysis of the RAPID trials. *RMD Open* 2016; 2(1): e000219.
22. Baker JF, Conaghan PG, Emery P, et al. Relationship of patient-reported outcomes with MRI measures in rheumatoid arthritis. *Ann Rheum Dis* 2017; 76: 486–490.
23. Wiese AB, Berrocal VJ, Furst DE, et al. Correlates and responsiveness to change of measures of skin and musculoskeletal disease in early diffuse systemic sclerosis. *Arthritis Care Res (Hoboken)* 2014; 66(11): 1731–1739.
24. Damjanov N, Radunovic G, Prodanovic S, et al. Construct validity and reliability of ultrasound disease activity score in assessing joint inflammation in RA: comparison with DAS-28. *Rheumatology (Oxford)* 2012; 51(1): 120–128.
25. Gordon JK, Girish G, Berrocal VJ et al. Reliability and validity of the tender and swollen joint account: analysis from the Prospective Registry of Early Systemic Sclerosis Cohort. *Journal of Rheumatology* 2017; 44: 791–794.
26. La Montagna G, Baruffo A, Tirri R, et al. Foot involvement in systemic sclerosis: a longitudinal study of 100 patients. *Semin Arthritis Rheum* 2002; 31(4): 248–255.
27. Varjú C, Péntek M, Lóránd V, et al. Musculoskeletal involvement in systemic sclerosis: an unexplored aspect of the disease. *J Scleroderma Relat Disord* 2017; 2(1): 19–32.
28. Wakefield RJ, Gibbon WW, Conaghan PG, et al. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. *Arthritis Rheum* 2000; 43: 2762–2770.