JSRD Journal of Scleroderma and Related Disorders

Review

Journal of Scleroderma and Related Disorders
1–10

DOI: 10.1177/2397198320970394
journals.sagepub.com/home/jso
SAGE

The role of ultrasound in systemic sclerosis: On the cutting edge to foster clinical and research advancement

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Abstract

Ultrasound has been widely explored in systemic sclerosis in the clinical and research settings. Ultrasound allows a non-invasive and ionising radiation-free 'window' into this complex disease and is well-suited to repeated examinations. Ultrasound provides novel insights into the pathogenesis and measurement of disease in systemic sclerosis, including early (preclinical) internal organ involvement. The purpose of this review is to describe the role of ultrasound to foster clinical and research advancements in systemic sclerosis relating to (1) musculoskeletal, (2) digital ulcer, (3) lung disease and (4) skin disease. We also highlight unmet needs which much be addressed for ultrasound to assume a central role in systemic sclerosis clinical care and research.

Keywords

Systemic sclerosis, scleroderma, ultrasound, musculoskeletal, digital ulcer, lung, skin

Date received: 17 August 2020; accepted: 5 October 2020

Introduction

Systemic sclerosis (SSc) is characterised by tissue fibrosis of the skin and other major internal organs, inflammation and autoimmunity and systemic vasculopathy.[1,2] Considering such broad-ranging pathology, using clinical assessment alone to define the presence and/or extent of the disease is often very challenging, especially in early disease. Ultrasound (US) allows a non-invasive and ionising radiation-free 'window' into this complex

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disease and is well-suited to multiple (repeated) examinations. The purpose of this review is to describe the role of US to foster clinical and research advancements in SSc relating to (1) musculoskeletal (MSK), (2) digital ulcer (DU), (3) lung and (4) skin involvement.

Methods

The breadth of this review was not amenable to a formal systematic literature review owing to the need to identify and appraise a broad range of sources of information for each of the four main topics. The different search approaches for the topics will be described within the body of the relevant sections.

MSK

Search strategy

We reviewed all relevant scientific articles regarding US in SSc published in the last 15 years, according to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines.[3]

We also performed a systemic research on electronic databases (PubMed and EMBASE) using the following search terms in all possible combinations: US, ultrasonography, sonography, SSc, tendons, joints and musculoskeletal. In addition, we evaluated all the articles concerning studies in humans, published between January 2005 and May 2020, removing duplicates. Two independent rheumatologists screened all the titles, abstracts and full reports of articles identified, and in case of disagreement, a third investigator was consulted, obtaining a consensus. Exclusion criteria were case reports, letters to the editor, non-human studies and articles not published in English.

Introduction

MSK involvement is common in patients with SSc and the clinical manifestations are highly variable, ranging from arthralgias to frank arthritis, contractures and tendon friction rubs (TFRs).[4] Joint symptoms are reported by 24%–97% of patients with SSc during the course of their disease[5,6] and are present in 12%–66% of patients at the time of diagnosis.[7,8] However, accurate clinical evaluation of MSK involvement in patients with SSc is often challenging, for example, due to extensive skin involvement and joint contractures.[4] Whereas, US allows the presence and extent of broad-ranging pathologies to be easily defined including (but not limited to) inflammatory abnormalities (synovitis, tenosynovitis and enthesitis), non-inflammatory disease and neuropathies.[4] Joint involvement is a major contributor to disability in SSc and synovitis and TFRs have been reported to be predictive of overall disease progression. Therefore, accurate characterisation of MSK involvement allows identification of high-risk patients of disease progression and poor outcome, with a view to early therapeutic intervention.[9]

Joints and tendons

MSK imaging can play an important role in identifying articular pathologies in patients with SSc, including in the absence of overt clinical signs of arthritis and non-inflammatory arthropathy (Figure 1).[4,10]

The high prevalence of US synovial involvement is well established in SSc, including foot involvement.[11–16] However, the presence of synovitis is significantly *underestimated* by clinical examination alone compared to US.[11,14–17] In a meta-analysis which included seven studies, the prevalence (95% confidence interval) of radiologically detectable (by plain radiography) and clinical arthritis was reported to be 26% (16.7, 36.1%) and 23% (14.9, 30.9%), respectively.[18] Similarly, inflammatory tendon disease is common in SSc and US is superior to clinical examination in detecting the presence of tenosynovitis.[12,16,19,20] For example, in the study by Chitale et al.,[17] which included 17 patients with SSc reporting arthralgia and no overt inflammatory arthritis on clinical examination, the prevalence of tenosynovitis at baseline and 6 months was 46% and 47%, respectively.[17]

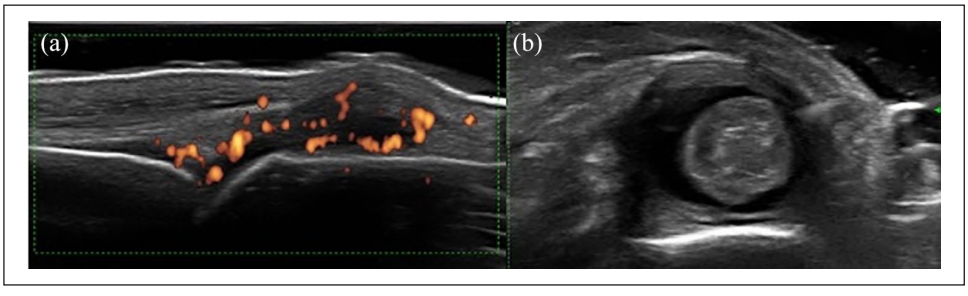

Figure 1. Inflammatory joint and tendon disease in SSc as assessed by MSK US. (a) Synovitis: metacarpophalangeal joint in dorsal scan showing synovitis with synovial proliferation and intra-articular power Doppler signal. (b) Tenosynovitis: transverse can of the tibialis tendon which demonstrates moderate tenosynovitis.

US has also revealed novel insights into the origin of TFRs in SSc.[4,10] Thickening of the wrist extensor and flexor tendons of the retinaculum and tenosynovitis has been proposed to be the morphological substrate of TFRs in SSc.[21,22] Increased A1 pulley thickness as assessed by US has been described in patients with SSc[23,24] and reported to correlate with impaired hand mobility.[23] Furthermore, in addition to A1 pulley thickening, localised peritendinous and soft tissue calcifications (as visualised by US) have been postulated to potentially play a role in the pathophysiology of SSc-hand contractures through causing mechanical impingement of the finger flexion mechanism.[24]

Enthesitis

Kilic et al.[25] conducted a cross-sectional single-centre study aimed to investigate the presence and distribution of enthesopathy in SSc. Patients with SSc had significantly higher Madrid sonographic enthesitis index (MASEI) scores than the healthy controls. In addition, the tendons and ligaments were thicker in the SSc group. There was a positive correlation between MASEI score and age, modified Rodnan skin score (mRSS) and severity of dyspnoea and a negative correlation with handgrip strength.[25] Terenzi et al.[26] conducted a cross-sectional study which sought to estimate the prevalence of entheseal and synovio-entheseal complex (SEC) alterations in SSc. Glasgow Ultrasound Enthesis Scoring System (GUESS) was significantly higher in patients than in healthy controls, including lateral epicondylar common extensor tendon (CET) enthesis. In addition, power Doppler (PD) CET enthesis, including SEC involvement, was significantly more frequent in patients with SSc compared to in healthy controls.[26] The authors remarked that the high frequency of enthesopathy in SSc, and in particular, CET enthesopathy was correlated with SEC inflammation, which could suggest that entheseal inflammation in SSc may share the same micro-anatomical targets observed in spondylarthritis.[26]

Nerves

Neurological complications in patients with SSc are mostly related to the entrapment neuropathies such as carpal tunnel syndrome and ulnar nerve entrapment at the elbow.[27,28] Median nerve dimensions, including area, have been reported to be increased in patients with SSc (even if asymptomatic)[29] and reduced nerve density has been observed particularly in symptomatic patients.[30] In a small, uncontrolled study which included 12 consecutive patients with SSc and intractable hand pain, US-guided carpal tunnel hydrodissection followed by corticosteroid injection was reported to reduce pain and improve digital vasculopathy (number of Raynaud's attacks and healing of ulcers).[31]

Summary of MSK US

MSK involvement in SSc is wide-ranging and is a significant cause of pain and disability associated with the disease. US allows novel insight into MSK complications including inflammatory and non-inflammatory disease, thereby allowing early identification and initiation of treatment.

Digital ulcers

A remarkable contribution of US in assessment of SSc-skin ulcers, as a tool to diagnose DU and to test therapy is recently noted. However, the degree to which US is validated for use in SSc DU should be ascertained. Without such validation, studies of treatment success/failure or diagnosis should be viewed very conservatively. For this reason, the state of validation of US for DU in SSc was examined.

A systematic literature review was undertaken to examine the validity of US for digital ulcers in SSc. The following search criteria were applied within the Cochrane Library, Web of Science and National Institutes of Health's National Library of Medicine (PubMed) to facilitate the identification of relevant manuscripts: '(systemic sclerosis OR scleroderma OR CREST) AND (ultrasound OR ultrasonography OR US) AND (ulcer* OR digital ulcer*)'. Two investigators examined the results and verified appropriate titles and abstracts according to pre-defined inclusion/exclusion criteria. When agreement was not achieved, a third investigator was consulted.

The titles and abstracts of journal articles identified from these searches formed the mainstay to identify the relevant work, alongside additional searches of the manuscripts cited within these articles for any missed, relevant published articles.

DU US

Hughes et al.[32] utilised high-frequency (35 MHz) US to examine a spectrum of DUs, including those on the fingertips, overlying the extensor (dorsal) aspects, and in relation to underlying subcutaneous calcinosis (Figure 2). The mean depth and width were 0.99 (0.45) and 5.74 (2.16) mm,[32] respectively, which highlight the inherent challenge of visual assessment of ulcers alone. Lower frequency (5–18 MHz) US has also been successfully utilised by Suliman et al. (Suliman, Kafaja and Fitzgerald, 2018) where they used both grey scale and PD signals, a skin ulcer was defined as (a) focal loss of epidermis and/or partial dermal loss or (b) focal loss of the epidermal layer and/or partial dermal loss and replacement by irregular hyperechoic tissue located below the level of the surrounding normal epidermis. Non-ulcer lesions were lesions of the epidermal layer that may appear as irregular hyperechoic tissue at the same level or above the level of the surrounding normal epidermis. Eight lesions were defined as

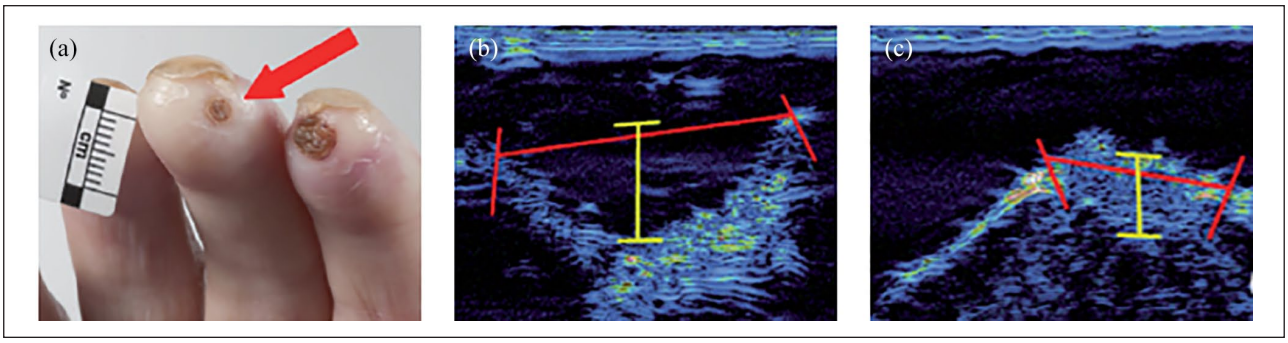

Figure 2. DU US. (a) Fingertip DU with high-frequency US images of the (b) 'long' and (c) 'short' axis indicating the ulcer width (red bars) and depth (yellow bars).
Adapted from Hughes et al.[32]

ulcers, 13 as non-ulcer lesions, 5 lesions showed underlying calcinosis and 3 ulcers showed higher PD signal.[33] Furthermore, the authors demonstrated that higher ulcer PD signal was likely due to infection and that antibiotic treatment was associated with improvement in ulcer-associated pain and Doppler signal.[33]

Unmet needs and limitations

There is evidence to support face validity of DU US in SSc.[32–37] Early data are also encouraging with evidence for content and criterion validity[35] and responsiveness.[36] However, neither construct validity nor discrimination have been adequately shown. One of the main current limitations is that DU US requires specialist training and equipment, thus limiting feasibility to centres with appropriate equipment and training, which is adequate for clinical trials. In clinical practice, practical use can be supported but its sensitivity/specificity in that setting has not been clearly documented. The potential for future wider-spread adoption exists although, in addition to the cost of the equipment and necessary training, factors such as the optimal frequency of the US probe is yet to be determined.

Summary of DU US

DU US has a very promising role in defining skin ulcers in patients with SSc and may support the assessment of DU morphology, extent and underlying pathology.[38] It can also, once fully validated, improve the ability to discover effective treatment for this very painful and function-limiting aspect of SSc. Future research is required to fully validate this modality and to optimise the technical aspects and other required requisites of this technique.

Lung

Search strategy

All relevant scientific articles were evaluated regarding interstitial lung disease (ILD) in SSc according to the PRISMA guidelines.[3] We performed a systematic research on the electronic databases (MEDLINE) using free terms and medical descriptions (e.g. MeSH terms) in all possible combinations: 'Ultrasonography', ultrasound, sonography, ultrasonography, 'Lung disease, interstitial', interstitial lung disease, interstitial fibrosis, interstitial pulmonary fibrosis, pulmonary fibrosis, 'Scleroderma, Systemic', scleroderma and systemic sclerosis. Articles that were already known to the authors of this review were also included. Research results were screened to avoid duplicates.

We evaluated all the articles concerning studies published between January 2005 and April 2020. Titles, abstracts and full reports of the identified articles were systematically screened concerning inclusion and exclusion criteria. A study was deemed eligible if it included at least one defined group of patients with SSc and reported a structured evaluation of the lung US (LUS). We excluded from this review articles not published in English, case reports, reviews, meta-analysis and non-human studies.

Introduction

Interstitial lung disease (ILD) is common in SSc and remains the major cause of death in these patients despite continuous advances in treatment.[39,40] Therefore, clinicians must remain constantly mindful of this potential complication and adopt an accurate strategy to detect ILD in the very earliest stages, with a view to close monitoring and/or therapeutic intervention.[40]

Imaging plays a key role in the management of SSc-ILD. Chest high-resolution computed tomography (HRCT) is currently considered to be the 'gold standard'/reference imaging technique that is used to establish the diagnosis of ILD and has important prognostic implications.[41] However, HRCT is unsuitable for frequent screening of the lung parenchymal modifications due to high costs, ionising radiation and ethical issues.[42] Our current approach to the assessment of SSc-ILD, which includes plain chest radiography, pulmonary auscultation and pulmonary function tests (PFT), is insensitive to detect early ILD. Therefore, as an effort to fulfil this gap, many authors have proposed

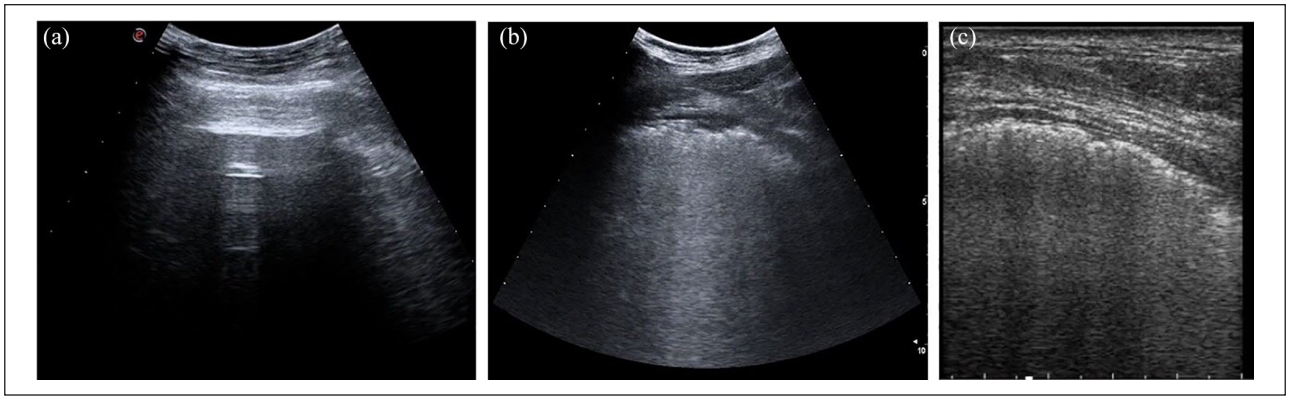

Figure 3. LUS in SSc. (a) Normal LUS. Advanced ILD (B-lines and pleural line alterations) using (b) convex and (c) linear probes.

LUS as an imaging technique that is able to assess SSc-ILD,[43–60] even in the earliest stages.[49,51]

Preliminary studies have demonstrated reasonable correlation between LUS and HRCT findings in the detection of ILD in established patients with SSc.[43] Following these observations, successive works have confirmed the utility of LUS in SSc-ILD, including adequate correlations with PFT and diffusion capacity of carbon monoxide (DLCO). In addition, US scoring systems, which quantify the severity of SSc-ILD, have been proposed.[53,61] The utility of LUS in the diagnosis of ILD in very early SSc[55] and more recently, its potential for the detection of SSc-ILD in asymptomatic preclinical stages[51] have also been described. Recent research has been focused on the predictive value of LUS,[50,52] which is opening new perspectives for the application of US as a screening method for SSc-ILD in clinical practice.

Although these compelling arguments for the role of LUS in SSc, currently there is no strong consensus regarding the role of LUS in the diagnosis and/or prognosis of SSc-ILD. Therefore, the main purpose of this section is to provide an overview of the potential role of the US in the assessment of SSc-ILD, including established and preclinical stages and to discuss the current evidence supporting its clinical applications in the daily clinical setting.

Methodological aspects

The main LUS signs for ILD-SSc assessment are B-lines and pleural line alterations (Figure 3). B-lines are defined as discrete laser-like vertical hyperechoic reverberation artefacts that arise from the pleural line[62] and can be evaluated by various types of transducers without any clinically important differences.[44] However, convex or phased-array probes are considered to be the best transducers to identify B-lines, especially for the purpose of quantification/semi-quantification. Whereas, pleural line alterations are better visualised by a linear or convex probe (Figure 3). Therefore, a convex (or microconvex) probe is probably the better choice to combine both types of assessments with one probe. The depth is usually set according to patient's size, to clearly visualise the pleural line and the focus should be at the level of the pleural line.

When B-lines can be identified singularly, they can be enumerated one by one. However, when they are confluent – which is often the case in more advanced stages of ILD – it is useful to assess the percentage of hyperechoic 'white' signal generated by B-lines below the pleural line and divide it by 10 (i.e. 60% of the 'white screen' below the pleural line would account for approximately six B-lines).[62,63]

Pleural line alterations are quite typical in SSc-ILD, especially in more advanced stages of the disease, whereas initial lung involvement can display only a few B-lines with no clear irregularities of the pleural line. The term 'pleural line alterations' should be preferred to 'thickened pleural line', because the sonographic depiction of the pleura is not its anatomical equivalent.

There is no universal definition for the scanning protocol to be used: over the years, different schemes including up to 72,[43] 50, 14,[53] and 10 scanning areas[57] have been used. However, it is crucial to combine high sensitivity with feasibility and a reasonable scanning time; if fewer areas are examined, then the LUS examination should focus on the posterior lung bases because SSc-ILD usually first develops in this region.

Clinical applications and future perspectives

The risk of developing ILD is higher in the first 5 years since SSc diagnosis. During this phase, an efficient screening tool should be extensively used to early detect lung abnormalities, which may be confirmed by HRCT, to start early a target treatment. Despite many technical differences (convex/linear and 2.5–10 MHz probes; scanning protocols considering 72–10 intercostal spaces; scoring systems; pathological B-lines cut-off),[43–50,53–60] LUS provides significant positive correlations between B-lines and HRCT findings and, less commonly, between B-lines and vascular damage (capillaroscopic pattern and number

of digital ulcers).[45,50] Literature data also describe a similar correlation between pleural line alterations ('US' thickness > 3 mm or irregularities) and HRCT, probably allowing a better discrimination than B-lines in ILD detection.[47,54,58–60] Therefore, a negative correlation has been demonstrated between B-lines and PFT (DLCO and forced vital capacity).[43,45,46,48] The potential prognostic utility was explored by Gasparini et al.,[50] who showed that basal B-lines predict DLCO change after 12 months and by Gargani et al.,[52] who demonstrated that a higher number of B-lines is associated with worsening or development of pulmonary involvement.

A systematic review by the Outcome Measures in Rheumatology (OMERACT) US group which included 12 (out of 300 identified) papers concluded that LUS passed the filter of face and content validity and feasibility; however, there was insufficient evidence to support criterion validity, reliability and sensitivity to change.[64]

To be effective, a screening tool requires both high sensitivity and a negative predictive value (NPV). LUS has both of these required prerequisites, in particular, B-lines show a sensitivity between 59% and 100% and NPV between 51.7% and 100%, while pleural line alterations have a sensitivity between 74% and 85%.[46,49,55–57] Furthermore, B-lines have been reported to have a high specificity and positive predictive value of 59%–99% and 90.6%–95.1%, respectively, as well as pleural lines abnormalities which have almost perfect specificity (99%–100%).[46,48,49,55–57,60] These wide ranges are possibly explained by the differences in the probes used (cardiac, convex or linear, with different frequencies) and number of scanned areas (10, 14 or 72).

Summary of lung US

LUS is a promising imaging technique to detect ILD in patients with SSc. Next steps for a wider applicability of LUS in the assessment of SSc-ILD are represented by technique standardisation (definition of the findings to be used, protocols of image acquisition and quantification of findings) and other 'clinical' needs (validation in early stages of the disease; evaluation of the optimal timing for diagnosis and follow-up; and minimal significant detectable change). Finally, promising results have been shown in ILD patients (including also SSc) for automatization of the scan evaluation[65,66] and of B-lines quantification.[67]

Skin

Search strategy

Studies eligible for inclusion needed to include at least one defined group of patients with SSc and report a structured evaluation of the skin by US and/or US elastography. Studies on animal models were excluded. All articles published up to April 2020 were considered for inclusion written in either English, Spanish, French, Italian or Portuguese language.

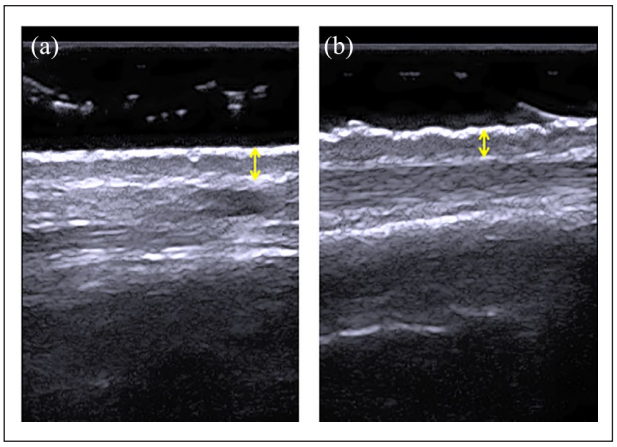

Figure 4. Skin US in SSc. Example of the measurement of dermal thickness (yellow arrows) by skin high-frequency US (22 MHz probe, Esaote, Genoa, Italy) in (a) a healthy subject and (b) a patient with SSc at the level of hand.

Background

Skin involvement is one of the cardinal features of SSc and significant interest has been focused on skin US which allows direct visualisation of the skin throughout the course of the disease and potentially addresses the challenges of assessment and interpretation of skin fibrosis in SSc.[68–70]

Skin US and elastography in SSc

Skin US is a reproducible technique to assess the extent of skin involvement and correlates well with clinical assessment, including in areas of skin defined as 'uninvolved' by the clinical palpation alone.[69,71,72] Several studies have demonstrated that patients with SSc have higher skin thickness[73–77] (Figure 4) and lower skin echogenicity than healthy controls by US,[77,78] including very early disease (<2 years)[78] and in diffuse compared to limited SSc and healthy controls.[79] An inverse relationship between skin echogenicity and thickness in SSc patients with shorter disease duration has been found, supposedly reflecting the oedematous phase of the disease.[80] The degree of skin thickening tends to diminish with longer disease duration.[74,75,77] A number of studies have showed a correlation between dermal thickness and the mRSS,[73,75,78] whereas others have not, particularly at the level of the phalanx.[74,81] Another study[22] reported a positive correlation between skin thickness of the middle phalanx and the total mRSS. The relationship between the degree of skin thickening as assessed by US and the severity of microangiopathy[73] and response to treatment (e.g. corticosteroids and cyclophosphamide) has been reported.[74,76]

US elastography has revealed a hard and scarcely elastic structure, which corresponds to the dermis in patients with SSc.[82] It has been proposed that US elastography could improve the reliability of US measurements of dermal thickness at the finger level in patients with SSc.[81] Several studies have assessed skin stiffness using shear-wave elastography[83–86] or qualitative colour-scale US elastography.[87] Overall, these studies found significantly higher shear-wave velocity values in SSc patients than in controls, at almost all of the Rodnan skin sites.[83–86] In addition, Yang et al.[83] reported that the skin stiffness as assessed by skin wave elastography was more sensitive to detect subtle skin changes than B-mode US. One important aspect relates to subclinical dermal involvement in SSc. The authors of two studies found that dermal thickness and skin stiffness were significantly higher in clinically uninvolved skin (i.e. with a mRSS score of 0) in SSc than in healthy controls.[86,88]

Zhang et al.[89] reported no correlation between skin viscosity, as evaluated by US surface wave elastography and the mRSS in 20 patients with SSc patients at either the left or right forearm and upper arm. Elastography has been reported to be more reproducible[90,91] and more sensitive[92] than mRSS in evaluation of the skin in SSc, the latter of which is in agreement with Li et al.[93] and Ruaro et al.[94] using US with 18 and 22 MHz probes, respectively, in patients with the limited subset of the disease. The 5-year follow-up study by Santiago et al.[95] reported a significant decrease in skin stiffness at all but finger level Rodnan sites in SSc patients compared to controls over time, which suggests that shear-wave elastography is more sensitive to time-related change than the mRSS.

Summary of skin US

Skin US and elastography are two non-invasive, operator-independent, imaging techniques that can be performed in 'real-time'. Studies to date are strongly encouraging and suggest that both imaging techniques could be readily adoptable tools to assess skin involvement in patients with SSc and are also potentially more sensitive than traditionally used clinical assessment alone, especially the mRSS.

Conclusion

In conclusion, US provides novel insights into pathogenesis and measurement of MSK, DU, lung disease and skin disease in SSc (Table 1). US has a clear role on the cutting edge to foster clinical and research advancement in SSc including the early detection and monitoring of internal organ involvement, and to drive the development of novel approaches to treatment. However, our work is not complete, and there are specific unmet needs within these US indications which must be addressed for US to assume a central role in SSc clinical care and research.

Table 1. The potential uses and measurements of US for MSK, DU, lung disease and skin disease in SSc.

MSK	Synovitis
	Tenosynovitis
	Non-inflammatory arthropathy
	Enthesitis
	Nerves
DU	DU dimensions – width and depth
	Doppler signal – infection and correlation with pain
	Associated pathology (e.g. calcinosis)
Lung	Pleural line alterations
	B-lines
Skin	Skin US – skin thickness, echogenicity
	US elastography

MSK: musculoskeletal; DU: digital ulcer.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

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

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References

1. Denton CP and Khanna DK. Systemic sclerosis. *Lancet* 2017; 390(10103): 1685–1699.
2. Hughes M and Herrick AL. Systemic sclerosis. *Br J Hosp Med* 2019; 80(9): 530–536.
3. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ Br Med J* 2015; 349: g7647.
4. Sandler RD, Matucci-Cerinic M and Hughes M. Musculoskeletal hand involvement in systemic sclerosis. *Semin Arthritis Rheum* 2020; 50(2): 329–334.
5. Avouac J, Guerini H, Wipff J, et al. Radiological hand involvement in systemic sclerosis. *Ann Rheum Dis* 2006; 65(8): 1088–1092.
6. Avouac J, Walker U, Tyndall A, et al. Characteristics of joint involvement and relationships with systemic inflammation in systemic sclerosis: results from the EULAR scleroderma trial and research group (EUSTAR) database. *J Rheumatol* 2010; 37(7): 1488–1501.
7. Baron M, Lee P and Keystone EC. The articular manifestations of progressive systemic sclerosis (scleroderma). *Ann Rheum Dis* 1982; 41(2): 147–152.
8. Avouac JPJC, Khanna D, Furst D, et al. Articular involvement in systemic sclerosis. *Rheumatology* 2012; 51(8): 1347–1356.

9. Avouac J, Walker UA, Hachulla E, et al. Joint and tendon involvement predict disease progression in systemic sclerosis: a EUSTAR prospective study. *Ann Rheum Dis* 2016; 75(1): 103–109.
10. 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.
11. Elhai M, Guerini H, Bazeli R, et al. Ultrasonographic hand features in systemic sclerosis and correlates with clinical, biological and radiographic findings. *Arthritis Care Res* 2012; 64(8): 1244–1249.
12. Cuomo G, Zappia M, Abignano G, et al. Ultrasonographic features of the hand and wrist in systemic sclerosis. *Rheumatology* 2009; 48(11): 1414–1417.
13. Iagnocco A, Vavala C, Vasile M, et al. Power Doppler ultrasound of the hand and wrist joints in systemic sclerosis. *Clin Exp Rheumatol* 2019; 31(2 Suppl. 76): 89–95.
14. Lescoat A, Ballerie A, Belhomme N, et al. Synovial involvement assessed by power Doppler ultra-sonography in systemic sclerosis: results of a cross-sectional study. *Rheumatology* 2018; 57(11): 2012–2021.
15. Karalilova R, Kazakova M, Sapundzhieva T, et al. Serum YKL-40 and IL-6 levels correlate with ultrasound findings of articular and periarticular involvement in patients with systemic sclerosis. *Rheumatol Int* 2019; 39(11): 1841–1848.
16. Hubac J, Gilson M, Gaudin P, et al. Ultrasound prevalence of wrist, hand, ankle and foot synovitis and tenosynovitis in systemic sclerosis, and relationship with disease features and hand disability. *Joint Bone Spine* 2020; 87(3): 229–233.
17. Chitale S, Ciapetti A, Hodgson R, et al. Magnetic resonance imaging and musculoskeletal ultrasonography detect and characterize covert inflammatory arthropathy in systemic sclerosis patients with arthralgia. *Rheumatology* 2010; 49(12): 2357–2361.
18. Schmeiser T, Pons-Kühnemann J, Özden F, et al. Arthritis in patients with systemic sclerosis. *Eur J Intern Med* 2012; 23(1): e25–e29.
19. Morrisroe KB, Nikpour M and Proudman SM. Musculoskeletal manifestations of systemic sclerosis. *Rheum Dis Clin North Am* 2015; 41(3): 507–518.
20. Gutierrez M, Pineda C, Cazenave T, et al. Ultrasound in systemic sclerosis: a multi-target approach from joint to lung. *Clin Rheumatol* 2014; 33(8): 1039–1047.
21. Cuomo G, Zappia M, Iudici M, et al. The origin of tendon friction rubs in patients with systemic sclerosis: a sonographic explanation. *Arthritis Rheum* 2012; 64(4): 1291–1293.
22. Stoenoiu MS, Houssiau FA and Lecouvet FE. Tendon friction rubs in systemic sclerosis: a possible explanation – an ultrasound and magnetic resonance imaging study. *Rheumatology* 2013; 52(3): 529–533.
23. Tagliafico A, Panico N, Serafini G, et al. The thickness of the A1 pulleys reflects the disability of hand mobility in scleroderma. *Eur J Radiol* 2011; 77(2): 254–257.
24. Hughes M, Manning J, Moore T, et al. Ultrasound findings in finger flexor tendons in systemic sclerosis: a cross-sectional pilot study. *J Scleroderma Relat Disord* 2019; 5(1): 77–82.
25. Kilic E, Kilic G, Akgul O, et al. Presence of enthesopathy demonstrated with ultrasonography in systemic sclerosis. *Mod Rheumatol* 2015; 25(5): 731–736.
26. Terenzi R, Karalilova R, Lepri G, et al. Enthesopathy and involvement of synovio-entheseal complex in systemic sclerosis: an ultrasound pilot study. *Rheumatology* 2020; 59(3): 580–585.
27. Amaral TN, Peres FA, Lapa AT, et al. Neurologic involvement in scleroderma: a systematic review. *Semin Arthritis Rheum* 2013; 43(3): 335–347.
28. Tagliafico A, Panico N, Resmini E, et al. The role of ultrasound imaging in the evaluation of peripheral nerve in systemic sclerosis (scleroderma). *Eur J Radiol* 2011; 77(3): 377–382.
29. Bandinelli F, Kaloudi O, Candelieri A, et al. Early detection of median nerve syndrome at the carpal tunnel with high-resolution 18 MHz ultrasonography in systemic sclerosis patients. *Clin Exp Rheumatol* 2010; 28(5 Suppl. 62): S15–18.
30. Bignotti B, Ghio M, Panico N, et al. High-resolution ultrasound of peripheral nerves in systemic sclerosis: a pilot study of computer-aided quantitative assessment of nerve density. *Skeletal Radiol* 2015; 44(12): 1761–1767.
31. DeLea SL, Chavez-Chiang NR, Poole JL, et al. Sonographically guided hydrodissection and corticosteroid injection for scleroderma hand. *Clin Rheumatol* 2011; 30(6): 805–813.
32. Hughes M, Moore T, Manning J, et al. A pilot study using high-frequency ultrasound to measure digital ulcers: a possible outcome measure in systemic sclerosis clinical trials. *Clin Exp Rheumatol* 2017; 35 (4): 218–219.
33. Suliman YA, Kafaja S, Fitzgerald J, et al. Ultrasound characterization of cutaneous ulcers in systemic sclerosis. *Clin Rheumatol* 2018; 37(6): 1555–1561.
34. Suliman Y, Ranganath V, Fitzgerald J, et al. Preliminary musculoskeletal ultrasound (MSUS) ulcer definition does not correlate with visual observation in systemic sclerosis (SSC) patients. *J Scleroderma Relat Disord* 2016; 1(1): 207, http://www.sclerodermajournal.com/article/46cc360c-dc9e-4030-98da-6b5da7f2a0b8 (accessed 25 November 2016).
35. Suliman YA, Kafaja S, Tawfik Y, et al. Criterion validity of ultrasound in characterization of skin ulcers in scleroderma. *J Scleroderma Relat Disord* 2018; 2018: 207, http://www.sclerodermajournal.com/article/46cc360c-dc9e-4030-98da-6b5da7f2a0b8
36. Frech T, Pierce J, Stoddard G, et al. Amniotic membrane dressings provide an effective treatment for systemic sclerosis digital ulcers. *Arthritis Rheumatol* 2019; 71(suppl. 10), https://acrabstracts.org/abstract/amniotic-membrane-dressings-provide-an-effective-treatment-for-systemic-sclerosis-digital-ulcers/ (accessed 15 August 2020).
37. Suliman Raganath V, Kafaja S and Furst D. Novel use of musculoskeletal ultrasound (MSUS) to measure ulcers in the skin of systemic sclerosis (SSc) patients. *Arthritis Rheum* 2015; 67(Suppl. 1): 2988.
38. Hughes M. Response to 'Ultrasound characterization of cutaneous ulcers in systemic sclerosis'. *Clin Rheumatol* 2018; 37(7): 2013.
39. Cappelli S, Bellando Randone S, Camiciottoli G, et al. Interstitial lung disease in systemic sclerosis: where do we stand. *Eur Respir Rev* 2015; 24(137): 411–419.
40. Hoffmann-Vold A-M, Maher TM, Philpot EE, et al. The identification and management of interstitial lung disease

in systemic sclerosis: evidence-based European consensus statements. *Lancet Rheumatol* 2020; 2(2): e71–83.
41. Bernstein EJ, Khanna D and Lederer DJ. Screening high-resolution computed tomography of the chest to detect interstitial lung disease in systemic sclerosis: a global survey of rheumatologists. *Arthritis Rheumatol* 2018; 70(6): 971–972.
42. Picano E, Semelka R, Ravenel J, et al. Rheumatological diseases and cancer: the hidden variable of radiation exposure. *Ann Rheum Dis* 2014; 73(12): 2065–2068.
43. Gargani L, Doveri M, D'Errico L, et al. Ultrasound lung comets in systemic sclerosis: a chest sonography hallmark of pulmonary interstitial fibrosis. *Rheumatology* 2009; 48(11): 1382–1387.
44. Delle Sedie A, Doveri M, Frassi F, et al. Ultrasound lung comets in systemic sclerosis: a useful tool to detect lung interstitial fibrosis. *Clin Exp Rheumatol* 2010; 28(5 Suppl. 62): S54.
45. Gigante A, Rossi Fanelli F, Lucci S, et al. Lung ultrasound in systemic sclerosis: correlation with high-resolution computed tomography, pulmonary function tests and clinical variables of disease. *Intern Emerg Med* 2016; 11(2): 213–217.
46. Çakir Edis E, Hatipoğlu ON, Pamuk ÖN, et al. Effectiveness of thoracic ultrasonography in the evaluation of the severity of pulmonary involvement in patients with systemic sclerosis. *Arch Rheumatol* 2016; 31(4): 364–370.
47. Buda N, Piskunowicz M, Porzezińska M, et al. Lung ultrasonography in the evaluation of interstitial lung disease in systemic connective tissue diseases: criteria and severity of pulmonary fibrosis – analysis of 52 patients. *Ultraschall Med* 2016; 37(4): 379–385.
48. Tardella M, Di Carlo M, Carotti M, et al. Ultrasound B-lines in the evaluation of interstitial lung disease in patients with systemic sclerosis: cut-off point definition for the presence of significant pulmonary fibrosis. *Medicine* 2018; 97(18): e0566.
49. Hassan RI, Lubertino LI, Barth MA, et al. Lung ultrasound as a screening method for interstitial lung disease in patients with systemic sclerosis. *J Clin Rheumatol* 2019; 25(7): 304–307.
50. Gasperini ML, Gigante A, Iacolare A, et al. The predictive role of lung ultrasound in progression of scleroderma interstitial lung disease. *Clin Rheumatol* 2020; 39(1): 119–123.
51. Reyes-Long S, Gutierrez M, Clavijo-Cornejo D, et al. Subclinical interstitial lung disease in patients with systemic sclerosis: a pilot study on the role of ultrasound. *Reumatol Clin* 2019; 7: S1699.
52. Gargani L, Bruni C, Romei C, et al. Prognostic value of lung ultrasound B-lines in systemic sclerosis. *Chest* 2020; 158: 1515–1525.
53. Gutierrez M, Salaffi F, Carotti M, et al. Utility of a simplified ultrasound assessment to assess interstitial pulmonary fibrosis in connective tissue disorders – preliminary results. *Arthritis Res Ther* 2011; 13(4): R134.
54. Moazedi-Fuerst FC, Zechner PM, Tripolt NJ, et al. Pulmonary echography in systemic sclerosis. *Clin Rheumatol* 2012; 31(11): 1621–1625.
55. Barskova T, Gargani L, Guiducci S, et al. Lung ultrasound for the screening of interstitial lung disease in very early systemic sclerosis. *Ann Rheum Dis* 2013; 72(3): 390–395.
56. Aghdashi M, Broofeh B and Mohammadi A. Diagnostic performances of high resolution trans-thoracic lung ultrasonography in pulmonary alveoli-interstitial involvement of rheumatoid lung disease. *Int J Clin Exp Med* 2013; 6(7): 562–566.
57. Mohammadi A, Oshnoei S and Ghasemi-rad M. Comparison of a new, modified lung ultrasonography technique with high-resolution CT in the diagnosis of the alveolo-interstitial syndrome of systemic scleroderma. *Med Ultrason* 2014; 16(1): 27–31.
58. Moazedi-Fuerst FC, Kielhauser S, Brickmann K, et al. Sonographic assessment of interstitial lung disease in patients with rheumatoid arthritis, systemic sclerosis and systemic lupus erythematosus. *Clin Exp Rheumatol* 2015; 33(4Suppl91): S87–91.
59. Sperandeo M, De Cata A, Molinaro F, et al. Ultrasound signs of pulmonary fibrosis in systemic sclerosis as timely indicators for chest computed tomography. *Scand J Rheumatol* 2015; 44(5): 389–398.
60. Pinal-Fernandez I, Pallisa-Nuñez E, Selva-O'Callaghan A, et al. Pleural irregularity, a new ultrasound sign for the study of interstitial lung disease in systemic sclerosis and antisynthetase syndrome. *Clin Exp Rheumatol* 2015; 33(4 Suppl. 91): S136–141.
61. Tardella M, Gutierrez M, Salaffi F, et al. Ultrasound in the assessment of pulmonary fibrosis in connective tissue disorders: correlation with high-resolution computed tomography. *J Rheumatol* 2012; 39(8): 1641–1647.
62. Volpicelli G, Elbarbary M, Blaivas M, et al. International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med* 2012; 38(4): 577–591.
63. Gargani L. Ultrasound of the lungs: more than a room with a view. *Heart Fail Clin* 2019; 15(2): 297–303.
64. Gutierrez M, Soto-Fajardo C, Carlos Pineda C, et al. Ultrasound in the assessment of interstitial lung disease in systemic sclerosis: a systematic literature review by the OMERACT ultrasound group. *J Rheumatol* 2020; 47(7): 991–1000.
65. Quarato CMI, Lacedonia D, Del Colle A, et al. Count of B-lines: a reappraisal. Comment on 'visual versus automatic ultrasound scoring of lung b-lines: reliability and consistency between systems'. *Med Ultrason* 2019; 21(2): 205–206.
66. Short J, Acebes C, Rodriguez-de-Lema G, et al. Visual versus automatic ultrasound scoring of lung B-lines: reliability and consistency between systems. *Med Ultrason* 2019; 21(1): 45–49.
67. Raso R, Tartarisco G, Matucci Cerinic M, et al. A soft computing-based B-line analysis for objective classification of severity of pulmonary edema and fibrosis. *JACC Cardiovasc Imaging* 2015; 8(4): 495–496.
68. Myers SL, Cohen JS, Sheets PW, et al. B-mode ultrasound evaluation of skin thickness in progressive systemic sclerosis. *J Rheumatol* 1986; 13(3): 577–580.
69. Akesson A, Forsberg L, Hederström E, et al. Ultrasound examination of skin thickness in patients with progressive systemic sclerosis (scleroderma). *Acta Radiol Diagn* 1986; 27(1): 91–94.
70. Brocks K, Stender I, Karlsmark T, et al. Ultrasonic measurement of skin thickness in patients with systemic sclerosis. *Acta Derm Venereol* 2000; 80(1): 59–60.

71. Ihn H, Shimozuma M, Fujimoto M, et al. Ultrasound measurement of skin thickness in systemic sclerosis. *Br J Rheumatol* 1995; 34(6): 535–538.
72. Moore TL, Lunt M, McManus B, et al. Seventeen-point dermal ultrasound scoring system – a reliable measure of skin thickness in patients with systemic sclerosis. *Rheumatology* 2003; 42(12): 1559–1563.
73. Sulli A, Ruaro B, Alessandri E, et al. Correlations between nailfold microangiopathy severity, finger dermal thickness and fingertip blood perfusion in systemic sclerosis patients. *Ann Rheum Dis* 2014; 73(1): 247–251.
74. Sedky MM, Fawzy SM, El Baki NA, et al. Systemic sclerosis: an ultrasonographic study of skin and subcutaneous tissue in relation to clinical findings. *Skin Res Technol* 2013; 19(1): e78–84.
75. Kaloudi O, Bandinelli F, Filippucci E, et al. High frequency ultrasound measurement of digital dermal thickness in systemic sclerosis. *Ann Rheum Dis* 2010; 69(6): 1140–1143.
76. Hashikabe M, Ohtsuka T and Yamazaki S. Quantitative echographic analysis of photochemotherapy on systemic sclerosis skin. *Arch Dermatol Res* 2005; 296(11): 522–527.
77. Akesson A, Hesselstrand R, Scheja A, et al. Longitudinal development of skin involvement and reliability of high frequency ultrasound in systemic sclerosis. *Ann Rheum Dis* 2004; 63(7): 791–796.
78. Hesselstrand R, Scheja A, Wildt M, et al. High-frequency ultrasound of skin involvement in systemic sclerosis reflects oedema, extension and severity in early disease. *Rheumatology (Oxford)* 2008; 47(1): 84–87.
79. Hesselstrand R, Westergren-Thorsson G, Scheja A, et al. The association between changes in skin echogenicity and the fibroblast production of biglycan and versican in systemic sclerosis. *Clin Exp Rheumatol* 2002; 20(3): 301–308.
80. Hesselstrand R, Carlestam J, Wildt M, et al. High frequency ultrasound of skin involvement in systemic sclerosis – a follow-up study. *Arthritis Res Ther* 2015; 17: 329.
81. Di Geso L, Filippucci E, Girolimetti R, et al. Reliability of ultrasound measurements of dermal thickness at digits in systemic sclerosis: role of elastosonography. *Clin Exp Rheumatol* 2011; 29(6): 926–932.
82. Iagnocco A, Kaloudi O, Perella C, et al. Ultrasound elastography assessment of skin involvement in systemic sclerosis: lights and shadows. *J Rheumatol* 2010; 37(8): 1688–1691.
83. Yang Y, Yan F, Wang L, et al. Quantification of skin stiffness in patients with systemic sclerosis using real-time shear wave elastography: a preliminary study. *Clin Exp Rheumatol* 2018; 36(4): 118–125.
84. Zhang X, Zhou B, Kalra S, et al. An Ultrasound surface wave technique for assessing skin and lung diseases. *Ultrasound Med Biol* 2018; 44(2): 321–331.
85. Liu H, Hou Y, Zhu Q-L, et al. A preliminary study of skin ultrasound in diffuse cutaneous systemic sclerosis: does skin echogenicity matter. *PLoS ONE* 2017; 12(3): e0174481.
86. Santiago T, Alcacer-Pitarch B, Salvador MJ, et al. A preliminary study using virtual touch imaging and quantification for the assessment of skin stiffness in systemic sclerosis. *Clin Exp Rheumatol* 2016; 34(5): 137–141.
87. Çildağ S and Çildağ MB. The relationship between the degree of skin fibrosis by sonoelastography and the degree of pulmonary involvement in scleroderma. *Turkish J Med Sci* 2017; 47(5): 1555–1559.
88. Sulli A, Ruaro B, Smith V, et al. Subclinical dermal involvement is detectable by high frequency ultrasound even in patients with limited cutaneous systemic sclerosis. *Arthritis Res Ther* 2017; 19(1): 61.
89. Zhang X, Zhou B and Osborn T. Ultrasound surface wave elastography for assessing scleroderma. *Ultrasound Med Biol* 2020; 46(5): 1263–1269.
90. Sobolewski P, Maślińska M, Zakrzewski J, et al. Applicability of shear wave elastography for the evaluation of skin strain in systemic sclerosis. *Rheumatol Int* 2020; 40(5): 737–745.
91. Yang Y, Qiu L, Wang L, et al. Quantitative assessment of skin stiffness using ultrasound shear wave elastography in systemic sclerosis. *Ultrasound Med Biol* 2019; 45(4): 902–912.
92. Aryan A, Alaeen H, Dadgostar M, et al. Sonoelastography for skin evaluation in sclerodermic patients. *Int J Prev Med* 2019; 10: 91.
93. Li H, Furst DE, Jin H, et al. High-frequency ultrasound of the skin in systemic sclerosis: an exploratory study to examine correlation with disease activity and to define the minimally detectable difference. *Arthritis Res Ther* 2018; 20(1): 181.
94. Ruaro B, Sulli A, Smith V, et al. The impact of transducer frequency in ultrasound evaluation of subclinical skin involvement in limited cutaneous systemic sclerosis patients. *Clin Exp Rheumatol* 2019; 37(4): 147–148.
95. Santiago T, Santiago M, Coutinho M, et al. How much of skin improvement over time in systemic sclerosis is due to normal ageing? A prospective study with shear-wave elastography. *Arthritis Res Ther* 2020; 22(1): 50.