

## RESEARCH ARTICLE

# Skin ultrasound in systemic sclerosis patients: An update

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### Abstract

Systemic sclerosis (SSc) is an autoimmune disorder of unknown etiology, characterized by vasculopathy and fibrosis of the skin and internal organs. Skin tightening is a clinical hallmark for the diagnosis of SSc and is used to classify subtypes of the disease. Skin involvement could also indicate disease course and mortality. There has been an increase in the use of skin high frequency ultrasound for the evaluation of dermal thickness and skin impairment in systemic sclerosis. Recently, ultrasound elastography has been used to evaluate the elastic properties of tissues in SSc patients. Furthermore, power Doppler ultrasound has been used to study the vascular impairment in SSc patients.

Herein we discuss the recent data from research and clinical practice on methods for the sonographic and ultrasound elastography evaluation of dermal thickness in systemic sclerosis. We also give brief overview of the evaluation of vascular damage by power Doppler ultrasound. The role of these techniques is still under debate and their use has not yet been fully validated.

### Keywords

Skin high frequency ultrasonography, ultrasound elastography, power Doppler ultrasound, systemic sclerosis, dermal thickness, skin fibrosis

## **Introduction**

Systemic sclerosis (SSc) is an autoimmune connective tissue disease, characterized by early microvascular damage and progressive fibrosis of internal organs and skin (1,2). Skin involvement in SSc is not only a hallmark for disease classification and activity but also has an inverse correlation with survival (3-5).

To date, the modified Rodnan skin score (mRSS) is the validated method to assess skin involvement. However, it has several limitations, including the fact that it cannot detect small but clinically relevant changes in skin thickness over time and has a high intra- and inter-observer variability (6-8). On the other hand, several studies have demonstrated that skin high-frequency ultrasound is a valid and reproducible technique to measure dermal thickness (DT) in scleroderma patients (9-17), thus progress in this area is expected with increasing developments in equipment technologies.

### **Skin high-frequency ultrasound.**

The first paper on skin high-frequency ultrasound was published by Alexander and Miller in 1979, where they reported their results using a 15 MHz transducer (18). This was followed by the availability of ultrasound machines equipped with higher frequency probes (i.e. 18-30 MHz), which allowed for a more widespread use of ultrasound for the study of skin thickness. In fact, these machines provide a better visualization of superficial skin structures, including epidermis, dermis and subcutaneous fat tissue, thus making it possible to make quantitative (i.e. thickness measurements) as well as qualitative (echostructure evaluation) assessments of the skin (4,9-15) in SSc patients. Several studies have compared the results obtained by ultrasound measurements to those of mRSS, the current gold standard for the study of skin impairment in SSc patients, reporting interesting correlations (11-15).

The mRSS and ultrasound have different advantages and limitations, i.e. the mRSS is influenced by skin thickness, texture and fixation, whilst high frequency sonography provides a more accurate DT assessment (6-8,10-14). Moreover, high frequency sonography also has the advantage of allowing for the identification of the different skin layers and offers a continuous range of DT values, differently from the semi-quantitative mRSS scale which has only 4 integer values (6-8,10-14). Despite ultrasound being a user-friendly and rapid-to-perform technique, it does have some drawbacks. Principally it is dependent on the operator's skills, including the application of the most appropriate scanning technique and the accurate interpretation of findings in this specific area (11-15).

However, sonography has various additional advantages. First of all, the images can be saved for further evaluation at a later stage. It also has an enhanced sensitivity in the detection of skin involvement in disease stages, as well as at follow-up, offering a valuable contribution to the clinical assessment of this disorder (10,13,14,19,20). Several studies have also demonstrated that skin high frequency ultrasound (18-30 MHz) can identify the oedematous phase that precedes palpable skin involvement in the early stage of SSc, supporting an early diagnosis of the disease (10,13,19). It has also been shown that high frequency ultrasound can identify subclinical diffuse dermal involvement in limited cutaneous systemic sclerosis (lcSSc) patients. In fact, higher DT was reported in 4/6 skin areas (arm, chest and abdomen) in lcSSc with normal mRSS (mRSS=0) than in healthy subjects (13). This is in contrast with the diagnosis of lcSSc, where skin involvement is confined to the extremities: hands, forearms, feet, legs and face (13).

A total of 50 lcSSc patients were enrolled into this study and 50 sex- and age-matched

healthy subjects. DT was evaluated by both mRSS and sonography at the usual 17 skin areas (zygoma, fingers, dorsum of the hands, forearms, upper arms, chest, abdomen, thighs, lower legs and feet) (13). The authors used an 18 MHz transducer and reported that it was more difficult to identify the different skin layers at the level of the thigh and upper arm than in the other areas (13). The same group of authors studied 48 lcSSc patients and 48 healthy subjects, matched for sex and age, and demonstrated that the DT evaluations performed with a 22 MHz probe were significantly higher than those obtained with an 18 MHz transducer in all the 17 areas analysed, both in lcSSc patients and healthy subjects (p-value <0.0001) (14). Moreover, the 22 MHz transducer detected a statistically significantly higher median DT (p-value <0.01) in all clinically unaffected skin areas for lcSSc patients, compared to controls. Whilst the 18 MHz transducer confirmed this finding in only 4 /6 body areas where the mRSS was normal (mRSS =0), in line with the diagnosis of lcSSc (arms, chest, and abdomen). A statistically significant positive correlation (p-value <0.0001) was observed between the results obtained with the two transducers in the DT evaluation and between each probe and the mRSS. Furthermore, the DT in lcSSc patients worsened as did the microangiopathy pattern (Early, Active and Late) (p-value<0.02). This study then suggested that a 22 MHz sonography probe is more sensitive in detecting subclinical DT changes than an 18 MHz probe. Furthermore, it confirmed that subclinical dermal involvement is detectable by skin high frequency sonography also in the clinically unaffected skin areas of lcSSc patients. In a recent prospective and cross-sectional study, Li et al confirmed that skin high frequency ultrasound was able to evaluate subclinical dermal involvement in 31 SSc patients and 31 age-matched and sex-matched healthy controls, using an 18-MHz

ultrasonic probe. Five different skin sites were studied: the dorsal of the right forearm 3 cm proximal to the wrist, the area between the II and III metacarpophalangeal joints of the right hand, the dorsal of the proximal phalanx of the right second finger, the skin of the right leg- 12 cm proximal to the ankle joint and the sternum- 2 cm distal to the upper part of the manubrium. The authors also demonstrated a positive correlation between skin damage and disease activity (19).

Moreover, a recent study by Naredo et al confirmed that high frequency sonography with a 50 MHz probe allows for a better resolution and visualization of the derma, providing a more accurate DT determination and a correct assessment of the different skin layers with a notable difference in dermis and hypodermis texture features between SSc and healthy subjects (20). In fact, three experts evaluated the DT at the level of forearm, hand and fingers in 21 SSc and in 6 healthy controls and concluded that DT was significantly higher in SSc patients than in the control group (p-value<0.05). Moreover, a texture computed analysis of the dermis and hypodermis was able to discriminate SSc from healthy subjects (area under the curve >0.07).The aforementioned observations are also in agreement with microarray gene expression studies, suggesting that clinically unaffected skin shares the peculiar gene signatures and pathology of clinically affected skin in SSc (21,22).

Another recent study on 8 lcSSc patients and 5 healthy subjects reported a positive correlation between the percentage of circulating fibrocytes, mRSS (p-value = 0.04) and DT-sonography, evaluated by both 22 MHz and 18 MHz probes ( $p < 0.05$ ) in lcSSc patients (23). This is an important observation, in as much as the migration of fibrocytes into inflammatory lesions and/or damaged tissues and their differentiation into myofibroblasts contributed to fibrosis through the secretion of essential ECM

proteins, primarily type I collagen and fibronectin. Furthermore, the results confirm that the percentage of circulating fibrocytes was higher in the lcSSc patients than in the healthy subjects (23). Moreover, the observation of higher  $\alpha$ SMA, COL-1 and TGF $\beta$ 1 gene expression in cultured lcSSc than in CNT fibrocytes ( $p < 0.01$ ) suggests that they have a propensity for transition into profibrotic activated myofibroblasts, the key cells involved in both tissue repair and fibrosis (23).

Other authors also reported correlations between skin sonography, mRSS and plicometer skin test when assessing skin damage in SSc patients (p-value  $< 0.0001$ ) (12). This study also confirmed a correlation between the severity of nailfold microangiopathy and the skin damage when evaluated by the three different methods used for the assessment of the cutaneous involvement (p-value  $< 0.01$ ) (12). Their findings confirm previous literature data that patients with lcSSc are likely to have less morphological and functional microvascular involvement than those with diffuse SSc (12, 24-28).

### **Ultrasound elastography.**

Ultrasound elastography (UE) is an innovative technique able to analyze the elastic properties of tissues in SSc patients. The first UE investigation was carried out in 2010, after other studies had demonstrated that it can enhance the assessment of fibrotic skin by ultrasound (16,29-33). A few recent studies have demonstrated the utility of UE in the investigation of skin impairment in SSc, with varying results on the correlations with sonography evaluation, which may well be due to the use of different equipment and software (4,16,29-32).

UE allows for the evaluation of tissue elasticity, which is decreased in SSc due to skin fibrosis and provides a colour scale that can be superimposed on the sonography grey

scale image. However, UE has similar drawbacks to ultrasound, requiring specific training and skills in the field (4,16,29-34).

The utility of UE in the assessment of skin in systemic sclerosis patients was first demonstrated by Iagnocco et al, in 2010 (29). The investigators enrolled 18 SSc patients and 15 healthy controls and reported that the imaging pattern observed at the level of forearm in SSc patients may represent a reduction of strain in the dermis due to loss of elasticity (29). Di Geso et al. observed that when UE was added to ultrasound in DT evaluation, there was an increase in the intra and inter-observer agreement of the sonography technique (intra-observer reliability ICC UE 0.979 vs ultrasound 0.904; inter-observer reliability ICC UE 0.881 vs ultrasound 0.726) (35).

A recent study by Grembiale et al used UE to evaluate skin stiffness in 20 SSc patients and demonstrated a strong relationship with microvascular alterations. It evidenced that diffuse SSc subjects had higher skin stiffness scores than both lcSSc and healthy subjects. Furthermore, the authors demonstrated an association between the late nailfold capillaroscopic pattern of microangiopathy and skin stiffness (p-value = 0.027) (36).

Recently, Santiago and colleagues carried out a 5-year follow-up where they assessed changes in skin stiffness in SSc patients using UE. The authors included 21 patients and 15 healthy controls. They observed a significant decrease in skin stiffness at all Rodnan sites (p-value  $\leq 0.001$ ), except at the finger level, in SSc patients and in controls over time. Furthermore, the investigators demonstrated that skin stiffness decreased significantly in 15/16 skin sites with local normal Rodnan at baseline, whereas the local Rodnan skin score changed significantly only in two areas, the upper arm (p-value= 0.046) and the forearm (p-value= 0.026). In conclusion, this study evidences that UE is

more sensitive to change over time than mRSS (38).

### **Power Doppler ultrasound.**

Recently, power Doppler ultrasound has also been used to assess the vascular impairment in SSc patients (39-40). These studies aimed at a comparison between microvascular damages on nailfold video-capillaroscopy (NVC) and macrovascular manifestations in SSc (39-40).

Schioppo et al. evaluated 106 SSc patients by NVC and power Doppler ultrasound, using a 22 MHz probe (39). They studied all the patients with the two techniques at the level of 3rd and 4th finger of the dominant hand, after exclusion of ulnar artery occlusion and observed that power Doppler ultrasound and NVC can provide different, but important, information as to macro- and micro-vascular involvement in SSc patients. Furthermore, these two aspects of vascular damage may not be present at the same time in every patient (39).

Recently, Lescoat et al studied 64 SSc patients and demonstrated that microvascular damage evaluated by NVC and macrovascular features, specifically ulnar artery occlusion assessed by power Doppler ultrasonography, showed a high association with the most important digital manifestations of SSc (digital ulcers, acroosteolysis, and calcinosis, (p-value <0.05). Noteworthy is the fact that ulnar artery occlusion and pathologic finger pulp blood flow, assessed by ultrasound, were associated with severe capillary loss evaluated by NVC (p< 0.05) (40).

### **Conclusion.**

In conclusion, recent literature has confirmed that the use of higher frequency probes (>22

MHz) is advisable for DT assessment as they are able to provide higher accuracy and sensitivity in the detection of subclinical skin involvement (10,13,14,19,20,41). Moreover, as recently reported, ultrasound elastography may also enhance the evaluation of fibrotic skin. Lastly, power Doppler ultrasound, equipped with a high frequency probes, can be useful for the evaluation of vascular damage in SSc (39,40).

Briefly, sonography is a promising technique that has a potential role in the evaluation of various tissues, even if further studies are warranted to establish its validity in such a complex disease as SSc.

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BR and AI contributed to the conception of the review and drafting of the manuscript. BR, AI, ADT contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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