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Review

Skin imaging in systemic sclerosis

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Abstract

Fibrotic involvement of the skin is a cardinal feature of systemic sclerosis (SSc). The extent of skin involvement is associated with internal organ involvement, coinciding with more severe disease course and poor prognosis. A palpation-based semi-quantitative score, the modified Rodnan skin score, is widely used for the assessment of skin involvement, but it is entailed by significant limitations. More objective approaches to measure skin involvement employing imaging have been explored continuously in the past decades and are currently advancing. Here, we review the use of different imaging techniques for the assessment of skin involvement in patients with SSc, focusing mainly on ultrasound, magnetic resonance imaging, and optical coherence tomography.

Key words: Imaging, systemic sclerosis, ultrasound, magnetic resonance imaging, optical coherence tomography, skin fibrosis

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by obliterative microvascular lesions and development of progressive cutaneous and internal organ fibrosis. Progressive skin thickening, characterized by variable extent and severity, is the key clinical feature of SSc. The extent of skin involvement is currently the major criterion for classifying SSc patients as diffuse or limited and is included in the ACR/EULAR classification criteria (1). More importantly, it predicts visceral involvement and decreased survival (2, 3).

Currently, the modified Rodnan skin score (mRSS) is the gold standard for the assessment of skin involvement in patients with SSc. The mRSS is based on clinical palpation and is a sum of scores from 0 (normal) to 3 (most severe) in 17 distinct areas of the body (4). Although mRSS is a fully validated method to measure the skin involvement, it has several limitations, requiring specific examiner skills and having varying experience between different observers (5, 6). Variations in subcutaneous fat and pinching force are only some of the variables that can affect the variability of the mRSS and contribute to misreading and errors. Moreover, the mRSS may not be sensitive enough to detect small but clinically relevant changes in skin thickness over time (7).

Ultrasound (US) has been used for more than 20 years in rheumatology. It has contributed to earlier diagnosis and more precise assessment of inflammatory arthritis (8). The usefulness of US to assess skin thickness in patients with SSc has been reported. Moreover, imaging of the elastic properties of skin using US elastography has become the subject of increasing research in patients with SSc.

A relatively new imaging technique using infrared light, optical coherence tomography (OCT), has driven the interest of rheumatologists in assessing and measuring skin fibrosis in SSc patients (9). Here, we explore the validity of imaging modalities, focusing on US, magnetic resonance imaging (MRI), and OCT, for skin involvement in SSc patients.

How ultrasound has evolved in measuring skin thickness

The normal skin is composed of the epidermis (ED) and dermis. The differentiation of interfaces with US was first introduced in 1979 by American orthopedic surgeons Alexander and Miller (10). They first used unfocused transducer with a resonant frequency of 15 MHz and calculated the distance between the skin surface and dermis/subcutaneous fat interface through a reflected signal amplitude versus time display. They compared the accuracy of this new US technique with a radiographic method of proven accuracy in which the skin on the radial aspect of the forearm was flattened against a wood block and an X-ray beam was projected. They first suggested that what they called an "ultrasonic biometric ruler" could be an accurate, simple, and non-invasive method for measuring thickness of human skin. In 1984, Serup J. measured the skin thickness of the forearm and skin-phalanx distance over the middle and proximal phalanges in 22 SSc

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patients using a 15 MHz ultrasound (A-scan) apparatus (11). The diameter of the transducer was only 5 mm, allowing measurement on the digits. Skin-phalanx distances were increased in patients with SSc compared with healthy controls (HCs).

In 1986, Myers et al. (12) studied the first B-mode US for determining skin thickness of patients with SSc. They used a prototype B-mode US scanner, designed as a research instrument for investigators (13). Using a 25 MHz transducer, they measured skin thickness over the volar surface of the forearm in two-dimensional cross-sectional images. They compared this result with an established radiographic technique. The results showed a high degree of correlation, demonstrating a potential application of B-mode US in the evaluation of skin thickness in patients with SSc. In the same year, Akesson and coworkers used 10 MHz B-mode US to measure skin thickness over the dorsal aspects of the proximal and middle phalanges of the second fingers in 40 SSc patients (14). Skin thickness in patients with SSc was increased compared with HC. Additionally, they re-evaluated the skin thickness after 6, 12, and 18 months in 14 SSc patients and measured thickness changes, showing the usefulness of US in assessing response to therapy over time (14).

The measurement of distance between the skin surface and skin-fat interface using a 30 MHz transducer built-in water bath also showed significantly increased skin thickness in patients with SSc (15). Interestingly, in this study, clinically uninvolved skin in SSc patients also showed increased thickness by US, although no thickened collagen bundles were found in the histology. Compared with HC, skin thickness on the forearms and/or the hands showed 64.6% sensitivity and 100% specificity for SSc (15).

In 1996, Seidenari and coworkers used a computer software to find image descriptors enabling characterization of sclerotic skin from normal skin (16). They found that echostructure, represented by echographic parameters referring to sclerotic skin, differed significantly between patients with SSc and HC. In 1997, Scheja et al. (17) measured skin thickness in 41 SSc patients and 41 HCs using 20 MHz US equipment. Skin thickness over the proximal phalanx of the right second finger and over the forearm was increased in patients with a disease duration of 2 years or less compared to HCs. Moreover, skin thickness correlated inversely with disease duration. No correlation with disease duration was found in the mean echogenicity. They also reported that US skin thickness correlated with mRSS at the hand and forearm.

In 2000, Brocks et al. (18) measured skin thickness in 20 SSc patients using 20 MHz US. They analyzed 5 sites: the proximal phalanx, metacarpal joint, 2 cm above the wrist and forearm, and the manubrium of sternum. The authors found increased skin thickness with an increasingly distal location of the arm only in patients with SSc but not in HCs. They also reported that the skin of Danish controls was sonographically thicker than the skin of Japanese controls, suggesting that skin thickness may vary with ethnic background. Interestingly, the correlation between skin thickness and mRSS was observed only at the proximal phalanx region. The authors explained this poor correlation with the fact that US measures the thickness of the skin, whereas mRSS is dependent on skin texture as well as on skin thickness (18).

In 2003, Moore and colleagues measured dermal thickness at 17 sites, corresponding to those assessed in the mRSS, using a 22 MHz transducer (19). The authors showed that the 17-point US scoring method is reliable and precise enough to detect small changes over time. They measured ED and dermal thickness separately by identifying skin surface and the ED/dermis and dermis/subcutis interfaces. In their study, the measurement precision was good for the dermis and poor for the ED. In 2004, Åkesson et al. measured skin thickness at five skin sites, estimated echogenicity by outlining a block of skin, and represented on an arbitrary scale of 0-255 pixels (20). They first demonstrated that US is able to detect different stages of diffuse SSc by measuring skin thickness with 1-4-year disease duration. The degree of thickening tended to diminish with time, and at 4 years, thickness was significantly decreased on the forearm and chest compared with the 1-year measurements. They also showed that, as SSc progressed from edematous to indurative stage, skin echogenicity increased in serial measurements.

Hashikabe and coworkers studied the effect of photochemotherapy in SSc patients by measuring dermal echointensity and dermal thickness using a 20 MHz transducer (21). The dermal echointensity after photochemotherapy significantly increased, while dermal thickness significantly decreased than before therapy. The authors concluded that quantitative analysis is a reliable method in evaluating changes of skin edema in SSc. In 2008, Hesselstrand et al. measured both skin thickness and echogenicity at five different anatomical sites in 106 SSc patients within 2 years from the first non-Raynaud's symptom and compared them with the mRSS (22). The authors reported that patients with short disease duration were characterized by high skin thickness and low skin echogenicity, which correlated inversely, reflecting edema The US skin thickness correlated to the local mRSS from the corresponding region and also to the total mRSS (22).

Kaloudi et al. (23) evaluated skin thickness in 70 patients with SSc at 2 different sites on the second digit of the dominant limb. Patients were divided into three subgroups according to the phase of the disease: edematous, fibrotic, and atrophic phase. They found that dermal thickness correlated with the clinical phase of skin involvement, and thickness was decreased as the clinical phase progressed from the edematous to atrophic phase. In contrast, in a study to assess the effect of bosentan for 24 weeks on skin fibrosis in 10 SSc patients, US skin thickness analysis could only show a slight and insignificant trend towards improvement despite significant changes in the mRSS (24). The authors speculated that this might have been due to the fact that the US examination could not be performed on exactly the same spot at each visit.

Inter and intraobserver variability of US skin thickness measurement

The epidermis is thicker on the palms, typically less than 0.1 mm thick (13). The overall dermal thickness varies from 0.5-3mm. Clear identification of the ED and dermis with US can be difficult by US. Moreover, the ED/dermis and dermis/subcutaneous tissue interfaces are not linear, which can influence the precision of measurement among investigators. Thus, the exact location of the electronic caliper at each interface is an important factor that determines the reliability in measuring skin thickness in B-mode US images. Previous studies have shown overall good intraobserver and interobserver variability. Scheja et al. reported interobserver variability of 1.0% for the proximal phalanx, 4.2% for the hand, and 0.0016% for the forearm by comparing the results obtained by two independent investigators, measuring the skin thickness over 4 different points in 10 controls (17). The precision of measurements at 17 sites by identifying the surface/ED, dermis/ED, and dermis/subcutis interfaces was also good at most sites (19). The interobserver variability ranged from 0.65 to 0.94, and intraobserver variability ranged from 0.55 to 0.96. Kaloudi et al. also assessed variability by 2 observers at 2 different sites on the second digit of the hand. They reported low intra- and interobserver variability (intraobserver ICC 0.92 and 0.96 at 2 sites, respectively; interobserver ICC 0.92 and 0.97) (23). Table 1 reports studies

Table 1. Studies that used US to measure skin thickness in patients with SSc

References	US frequency and mode	Examination site (number enrolled)	Major findings
(Alexander and Miller 1979) (10)	15 MHz A mode	radial aspect of forearm (n=10 normal adults)	➢ "Ultrasonic biometric ruler" can provide accurate, simple method for measuring skin thickness
(Serup 1984) (11)	15 MHz A mode	dorsum and volar surface of the forearm dorsum proximal and middle phalanx of the 3rd finger (n=22 SSc, 22 HC)	➢ Skin-phalanx distances were increased in patients with SSc compared with the controls
(Myers et al. 1986) (12)	Prototype 25 MHz B mode	volar surface of the forearm (n=8 SSc, 14 HC)	➢ B-mode US skin thickness correlated with skin thickness assessed by an established radiographic technique ➢ B-mode US has a potential application in the diagnosis and serial evaluation of skin thickness in patients with SSC
(Akesson et al. 1986) (14)	10 MHz B mode (DRF12®, Diasonics)	dorsum proximal and middle phalanx of 2nd finger (n=40 SSc, 10 HC)	➢ US skin thickness was thicker in patients with SSc compared with the HCs ➢ US skin thickness did not correlated with disease duration ➢ US can show skin thickness changes in serial evaluations of treatment
(Ihn et al. 1995) (15)	30 MHz B mode (UX-01®, Rion Co. Ltd. Tokyo, Japan)	dorsum of forearm, dorsum of hand, chest (n=79 SSc, 81 HC)	➢ Increased skin thickness of the forearms and/or hands showed 64.6% sensitivity, 100% specificity ➢ Clinically uninvolved skin in patients with SSc also showed increased thickness
(Seidenari et al. 1996) (16)	20 MHz combined A and B mode (DermaScanC®, Cortex Technology, Hadsund Denmark)	dorsum of the hand, forehead, cheek (n=18 SSc, 20 HC)	➢ Echostructures represented by values referring to sclerotic skin differed between the skin of patients with SSc and the controls
(Scheja and Akesson 1997) (17)	20 MHz, combined A and B mode (Dermascan®, Cortex technology, Hadsund, Denmark)	middle forearm, dorsum between 2nd and 3rd metacarpal of hand, dorsum mid-proximal phalanx of 2nd finger (n=41 SSc, 41 HC)	➢ US skin thickness was increased over the proximal phalanx and forearm in patients with a disease duration of 2 years or less ➢ Forearm US skin thickness inversely correlated to disease duration ➢ US skin thickness measurement showed an interobserver variability of 1.0% for the proximal phalanx, 4.2% at the hand, and 0.06% for the forearm ➢ US skin thickness was correlated with hand's and forearm's mRSS ➢ The echogenicity of either forearm and phalanx was not correlated with disease duration
(Brocks et al. 2000) (18)	20 MHz, combined A and B mode (Dermascan®, Cortex Technology, Hadsund, Denmark)	dorsum 3rd proximal phalanx, dorsum between 2nd and 3rd metacarpophalangeal joint, dorsum 2 cm above wrist, dorsum middle forearm, manubrium of sternum (n=20 SSc, 20 HC)	➢ US skin thickness increased with an increasingly distal location of the region studied only in patients with SSc but not in the controls ➢ US skin thickness correlated with the mRSS only at the proximal phalanx region not at other sites.
(Moore et al. 2003) (19)	22 MHz B mode (Diascus®, Dynamic Imaging Ltd, Livingston, Scotland)	17 sites corresponding to those assessed in the mRSS (n=39 SSc, 34 HC)	➢ The 17-point dermal US scoring system was extremely reliable ➢ US dermal thickness measurement at the 17 sites showed intraobserver variability of 0.65–0.94 and interobserver variability of 0.55–0.96
(Akesson et al. 2004) (20)	20 MHz combined A and B mode (Dermascan®, Cortex Technology, Hadsund, Denmark)	dorsum proximal phalanx of the 2nd finger, dorsum between 2nd and 3rd metacarpal joint,	➢ US skin thickness could show decreased skin thickness in repeated measurements at 2-4 years in diffuse SSc patients

Table 1. Studies that used US to measure skin thickness in patients with SSc (Contuinued)

		dorsum 3 cm proximal of the wrist, lateral 12 cm proximal of the ankle joint, sternum 2 cm distal form manubrium (n= 16 SSc, 16 HC)	➢ Echogenicity of hand skin echogenicity increased after 4 years in hand
(Hashikabe et al. 2005) (21)	20 MHz B-mode (DermaScanC®, Cortex Technology, Hadsund, Denmark)	dorsum distal 1/3 of forearms, central site of hand and finger (n=13 SSc)	➢ Quantified echointensity ranging from 0 to 100 was a reliable method in evaluating the change of skin edema in patients with SSc.
(Hesselstrand et al. 2008) (22)	20 MHz combined A and B mode (Dermascan®, Cortex Technology, Hadsund, Denmark)	dorsum 2nd proximal phalanx, dorsum between 2nd and 3rd MCP joint, dorsum 3cm above wrist, lateral 12 cm proximal of ankle joint, sternum 2 cm distal from manubrium (n=106 SSc)	➢ US skin thickness correlated inversely with skin echogenicity ➢ US skin thickness correlated with the local mRSS at the corresponding region and with the total mRSS
(Kaloudi et al. 2010) (23)	6-18 MHz B-mode mode (My Lab 25®, Esaote, Genoa, Italy)	two sites on the 2nd digit of dominant limb (n=70 SSc)	➢ US dermal thickness correlated with the total mRSS ➢ US dermal measurement showed an intraobserver variability of 0.92–0.96 and interobserver variability of 0.92–0.97 ➢ US skin thickness correlated with the clinical phase of skin involvement

HC: healthy controls; MCP: metacarpophalangeal; mRSS: modified Rodnan skin score; SSc: systemic sclerosis; US: ultrasound

that have previously used US to assess skin in SSc patients. Future studies should aim to standardize US assessment of skin in SSc patients, defining the technique, timing, and sites to be scanned.

US elastography

US elastography is a novel US application to analyze tissue elasticity. Among many variations of US elastography, freehand palpation elasticity imaging, which applies repetitive light manual compression and relaxation of the US probe against the tissue, is used in evaluating SSc patients (25). It requires no extra hardware and is based on a fast-processing software algorithm. US elastography has been used in other areas, including oncology and hepatology, helping in the detection and differentiation of malignant lesions and fibrosis (26-32).

In patients with SSc, the first investigation of the role of US elastography was reported by Iagnocco and coworkers in 2010 (33). Their study included 18 patients with SSc, with or without clinically detectable skin involvement. US elastography of the middle forearm showed the presence of a homogeneous blue color area corresponding to harder or fibrotic dermis. In contrast, no blue pattern was ever detected in the controls. Nevertheless, digital evaluation with US elastography showed color variability, suggesting that this technique may not be a reliable tool to evaluate the tissue elasticity of fingers affected by SSc. Recently, Filippucci and coworkers demonstrated that US elastography can improve the reliability of US in measuring dermal thickness at the finger level in patients with SSc (34). In their study, the interobserver and intraobserver variability of measuring skin thickness by US at the finger level improved when elastography was additionally adopted.

It seems that US elastography can provide a novel aspect in assessing fibrotic skin. However, owing to the lack of studies performed in patients with SSc, more comprehensive and extended data on the evaluation of SSc skin should be reported.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a successful tool for the morphological, metabolic, and functional evaluation of almost all organs and tissues of the body, except for the skin, in which, despite the significant advances, the spatial resolution still remains a challenge partially due to the intrinsic limitations of the skin-air interface.

Magnetic resonance imaging was first used and developed for skin in 1990 (35) but has not been widely used in dermatology and in rheumatic skin diseases, such as SSc. Recent studies regarding ^{23}Na magnetic resonance imaging-determined tissue sodium speculated that the increasing skin Na^+ coincided with increasing glycosaminoglycan content in skin and that Na^+ concentrations can be quantified noninvasively in skin (36). Of interest, a recent study demonstrated the feasibility of a highly sensitive superconducting surface coil for microscopic MRI of the human skin in vivo in a clinical 1.5 Tesla scanner (37). The authors obtained in vivo skin images with isotropic 80-µm resolution, revealing fine anatomical structures of the skin, such as the different skin layers: epidermis, dermis, and hypodermis. Also, small cutaneous vessels in the dermis and hypodermis were identifiable. For larger vessels >1 mm in diameter, the vessel walls could also be visualized. This technique could potentially have a role in assessing SSc skin, although the feasibility is questionable due to its cost and time consumption in clinical practice (38). More powerful magnets, now available in only a few research centers, might be able to produce higher spatial and contrast resolution skin images in the near future.

Opitical coherence tomography

Optical coherence tomography is an emerging imaging technique, recently shown to act as a virtual skin biopsy, with potential application in skin assessment in patients with SSc (9). It is a non-invasive imaging modality, similar in principle to US, but it measures the intensity of backscattered near-infrared light rather than acoustic waves (39). The common depth resolution is on the order of 5-10 µm, and the penetration depth is approximately 2 mm. OCT complements other imaging techniques, covering, in resolution and penetration, the gap between high-resolution optical microscopy

techniques (e.g., confocal microscopy) and techniques with long penetration depth (e.g., US imaging) (40).

Starting from 1991, OCT has progressively revolutionized medical imaging in ophthalmology, and nowadays, it is a clinical standard for the diagnosis and the follow-up of many eye diseases. The continuous technological improvements of the OCT system and the increasing demand of imaging tools for both diagnosis and response to therapy have driven the interest of many other fields of medicine, such as cardiology, urology, gastroenterology, pneumology, gynecology, neurology, dentistry, and dermatology (39, 41).

The use of OCT technology for quantification of skin fibrosis is in the formative stages, and a tremendous growth potential has been foreseen, similar to the ultrasound development paradigm that has evolved over the past 30 years (42). Until now, OCT has been applied to SSc skin assessment in one single-center study (9). Our group studied SSc skin by OCT, aiming to detect and quantify skin fibrosis using a Swept-Source OCT system. We included 21 SSc patients with different severities of skin involvement, 1 morphea patient, and 22 HCs. We compared the findings with histology from 3 skin biopsies, correlated them with mRSS, and assessed intra- and interobserver reliability.

In healthy skin, the ED appeared as a hypo-reflective layer compared to the underlying papillary dermis (PD). The different reflective properties allowed the easy identification of the dermal-epidermal junction (DEJ). The reticular dermis (RD) presented as a hypo-reflective region below the PD. Blood vessels were visible in the PD and RD as signal-poor cavities. In severely involved SSc skin, the dermis had a homogeneous aspect, and the epidermis appeared less hypo-reflective than in normal skin. Visualization of the DEJ was difficult. There was no clear distinction of the PD and RD. Only rare vessels were visualized compared with normal skin. Comparison of OCT images with corresponding skin histology indicated a progressive loss of visualization of the DEJ associated with dermal fibrosis.

Furthermore, SSc-affected skin showed a consistent decrease of optical density (OD) in the PD, which was progressively worse in patients with worse mRSS. Additionally, clinically unaffected skin was also distinguishable from healthy skin for its specific pattern of OD decrease in the RD. OCT analysis of affected and unaffected skin in a patient with plaque morphea showed a similar pattern of severe SSc and HC, respectively. In addition, the technique showed excellent intra- and interobserver reliability (9). Because of the very recent application of OCT in SSc and in a single-center study, there are currently several limitations to its applicability, ranging from the cost of the machine and the lack of standardization of the number and sites to study to the lack of evidence of sensitivity to change over time (38). Longitudinal studies including a larger number of patients with different degrees of fibrosis will eventually confirm the value of OCT as a surrogate marker of skin involvement in SSc.

Limitations of the current validated outcome measures for skin assessment in SSc have driven the interest towards relatively new imaging techniques. Several US studies and the proposal of novel tools, such as US elastography, MRI, and OCT, in this field are promising steps for the development of new imaging-based surrogate outcome measures of skin assessment in SSc. The development of more advanced technologies and sophistication of current hardware poise the imaging field to great future development in this direction.

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