A Preliminary Study of Acoustic Radiation Force Impulse Quantification for the Assessment of Skin in Diffuse Cutaneous Systemic Sclerosis

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ABSTRACT. ***Objective.*** To investigate skin elasticity using acoustic radiation force impulse (ARFI) quantification in systemic sclerosis (SSc), and compare the modified Rodnan skin score (mRSS) with measured shear wave velocity (SWV) and thickness of the skin.

Methods. Fifteen patients with diffuse cutaneous SSc (dcSSc) and 15 age-matched and sex-matched healthy controls were evaluated. The SWV and thickness of skin were measured at 17 sites corresponding to those assessed in the mRSS in each participant. The SWV measurements of skin were compared between patients with dcSSc and healthy controls. The correlations between the mRSS and the skin SWV and thickness were explored using Spearman's correlation.

Results. The SWV values were higher in patients with dcSSc compared with healthy controls at right hand dorsum, right forearm, left hand dorsum, left forearm, right foot dorsum, and left foot dorsum ($p < 0.05$). In patients with dcSSc, the SWV values of uninvolved skin were higher than those of controls ($p < 0.001$), and the SWV values increased with increasing skin scores except for skin score 3 ($p < 0.05$). The sum of the SWV values correlated with total clinical skin score ($r = 0.841$, $p < 0.001$), and the sum of the skin thickness correlated with total clinical skin score ($r = 0.740$, $p = 0.002$).

Conclusion. ARFI quantification is feasible and reliable for assessing the skin involvement in dcSSc. ARFI quantification could identify early skin change that may precede palpable skin involvement, and may be a valuable adjunct to skin evaluation in patients with SSc. (J Rheumatol First Release Jan 15 2015; doi:10.3899/jrheum.140873)

Key Indexing Terms:
SYSTEMIC SCLEROSIS SKIN INVOLVEMENT
ACOUSTIC RADIATION FORCE IMPULSE QUANTIFICATION

In systemic sclerosis (SSc), skin involvement is the characteristic manifestation. It can range from edema to fibrosis and eventually atrophy because of excessive dermal deposition of collagen and changes in the architecture of connective tissue[1]. Several studies have shown that the extent of skin involvement predicts internal organ involvement and the general outcome of patients[2,3]. The semiquantitative assessment of skin thickness by palpation (modified Rodnan skin score, or mRSS) is widely used in SSc, and it has been validated as a useful clinical trial outcome measure. Limitations of mRSS are interobserver variability[1,4], low sensitivity to change[5], and inability to distinguish between hard, tight, or thick skin[1,3,6].

High-frequency ultrasound (US) has been suggested for the determination of skin thickness and echogenicity[1,5]. It allows recognition of small and serial changes in the extent and nature of skin involvement, and makes possible the detection of different stages (edema, fibrosis, and atrophy) of the disease[5]. However, it is not useful for the assessment of skin elasticity. The elastography US (EUS) allows the assessment of tissue elastic properties, and several approaches including strain EUS, shear wave EUS, acoustic radiation force EUS, and transient EUS are now used in clinical practice[7]. US elastography in the assessment of skin involvement in SSc was first studied by Iagnocco, *et al* in 2010[8]. In their study, strain EUS technique was used and 2 sites, forearm and fingers, were evaluated. With strain EUS, the examiner applies manual probe compression to induce

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soft deformation, and the image produced is shown in color scale from red to blue, where red was used for soft tissues, blue for hard tissues, and yellow/green for tissue of intermediate stiffness. This method is qualitative rather than quantitative, and might be operator-dependent. In contrast, acoustic radiation force impulse (ARFI) imaging[7,9,10] provides quantitative information on tissue elasticity by measuring shear wave velocity (SWV) in a region of interest[11]. With this mode, instead of using external compression, US scanners are used to generate short-duration acoustic radiation forces that impart small (1–10 μm) localized displacements in the tissue[8,9], leading to the propagation of shear waves traveling in a direction perpendicular to the push pulse. SWV depends on tissue stiffness: the stiffer the tissue, the faster the shear waves propagate. Thus, ARFI imaging gives direct quantitative information about tissue elasticity properties and is less susceptible to examiner bias. To our knowledge, the role of ARFI quantification over 17 skin sites in patients with SSc has not been studied. The purpose of this study was therefore to investigate the performance of ARFI quantification in patients with dcSSc, and to compare the modified Rodnan skin score (mRSS) with ARFI quantification and US-measured skin thickness.

MATERIALS AND METHODS

Patients. The study protocol was approved by the ethics committee of Peking Union Medical College Hospital, and informed consent was obtained from all the participants. Fifteen patients with dcSSc, who all fulfilled the American College of Rheumatology criteria for the classification of SSc[12] and dcSSc[13], and 15 healthy controls, matched for age and sex, were prospectively included for the study. All patients were consecutively recruited at the Rheumatology Department of Peking Union Medical College Hospital between March 2013 and December 2013. At entry, all patients with dcSSc underwent clinical and serological assessment. A clinical summary of the enrolled patients with SSc is shown in Table 1. The mRSS over 17 anatomical sites was determined in each patient by an experienced physician who was trained at the European League Against Rheumatism Scleroderma Trials and Research group course and was unaware of the result of US assessment.

US examination. The 17 sites were identified according to the study by Moore, *et al*[14] and numbered as follows: site 1, 5: right and left middle finger (dorsum of middle phalanx); site 2, 6: right and left hand dorsum (index/middle metacarpal interspace, 2 cm proximal to the metacarpophalangeal joints); site 3, 7: right and left forearm (anterior aspect, 10 cm proximal to the ulnar styloid); site 4, 8: right and left upper arm (anterior aspect, 10 cm proximal to the medial epicondyle); site 9: forehead center; site 10: anterior chest (between sternal angle and notch); site 11: anterior abdomen (10 cm distal to the sternum); site 12, 15: right and left thigh (10 cm proximal to the patella); site 13, 16: right and left lower leg (anterolateral aspect, 10 cm proximal to the lateral malleolus); site 14, 17: right and left foot dorsum (in the first web space 2 cm proximal to the metatarsophalangeal joints). Skin thickness and SWV over the 17 sites were measured by US. A Siemens S2000 US system (S2000; Siemens Medical Solutions Inc.) equipped with an 18L6 MHz linear transducer for conventional US and a 9L4 MHz linear transducer for ARFI quantification (using Virtual Touch tissue quantification) was used. The transducer was placed in transverse section and perpendicular to the skin. A layer of gel was applied to maintain a minimal compression from the transducer to the skin, to improve ARFI imaging quality[15]. The quality criterion for acceptance of an US image was the adequate depiction of epidermis, dermis, and subcutis; as well, the interfaces between them had to appear distinct and parallel.

Skin thickness, including epidermis and dermis, was measured on the conventional greyscale image by 1 US physician (HL) using the 18L6 MHz linear transducer. SWV of the skin was independently measured by 2 US physicians (Q-LZ, HL) using the 9L4 MHz linear transducer. The SWV measurements were performed 5 times at the same location. When "X" displayed on the monitor, the measurements were interpreted as invalid. The 5 consecutive SWV measurements with no "X" result were used to calculate the mean for the statistical analysis.

Statistical analysis. SPSS software version 14.0 (SPSS) was used for statistical analysis, with $p < 0.05$ considered statistically significant. Data were expressed as median (lower quartile, upper quartile). The intraclass correlation coefficient (ICC) was calculated to examine the interobserver reliability of ARFI quantification. Differences in SWV and skin thickness between the patients with dcSSc and controls were assessed by Mann-Whitney U test. Among subgroups with different mRSS values, the SWV and skin thickness were compared using Kruskal-Wallis tests. Associations between variables were analyzed using Spearman's correlation.

Table 1. Clinical data of 15 patients with dcSSc.

Characteristic	
Patients age, yrs, mean ± SD	53.57 ± 8.22
Sex, female:male	10:5
Disease duration, mos, median (range)	54.7 (10–108)
Antitopoisomerase antibodies (+/–)	8/7
Anticentromere antibodies (+/–)	0/15
ANA (+/–)	13/2
mRSS, median (range)	11.3 (4–23)

dcSSc: diffuse cutaneous systemic sclerosis; ANA: antinuclear antibody; mRSS: modified Rodnan skin score.

RESULTS

Patients with dcSSc showed increased SWV at sites 2 (right hand dorsum), 3 (right forearm), 6 (left hand dorsum), 7 (left forearm), 14 (right foot dorsum), and 17 (left foot dorsum; $p < 0.05$) compared with healthy controls. The interobserver reliability of ARFI quantification was good for sites 2–4 and 6–17 (ICC 0.613–0.916), moderate for site 5 (left middle finger, ICC 0.535), but poor for site 1 (right middle finger, ICC 0.247). Table 2 outlines the SWV measurements of patients and controls and the interobserver variability of ARFI quantification. The SWV was 1.630 (1.420, 1.895) m/s for controls; 1.870 (1.505, 2.440) m/s for mRSS 0; 2.390 (1.800, 2.760) m/s for mRSS 1; 2.600 (2.220, 2.880) m/s for mRSS 2; and 2.960 (1.750, 3.865) m/s for mRSS 3 (Figure 1). The SWV of mRSS 0, 1, and 2 were significantly higher than those of controls ($p < 0.001$, 0.001, < 0.001, respectively). Significant difference existed between mRSS 0 and 1, mRSS 0 and 2 ($p = 0.001$, < 0.001, respectively). However, no significant difference was found between mRSS 3 and 0, 1, or 2.

The US-measured skin thickness was significantly higher in patients with dcSSc than in healthy controls at sites 1 (right middle finger), 2 (right hand dorsum), 3 (right forearm), 5 (left middle finger), 6 (left hand dorsum), 7 (left forearm), and 14 (right foot dorsum). The skin thickness

Table 2. The shear wave velocity (SWV) measurements of patients and controls and the interobserver variability of ARFI quantification.

Site**	SWV (m/s)			Interobserver Variability	
	Patients	Controls	p	ICC	p
1	2.146 (1.232, 2.598)	2.206 (1.763, 2.504)	0.668	0.247	0.205
2*	1.912 (1.811, 2.812)	1.308 (1.110, 1.464)	< 0.001	0.7	< 0.001
3*	2.703 (2.267, 2.900)	1.727 (1.421, 2.128)	< 0.001	0.913	< 0.001
4	1.562 (1.407, 1.885)	1.596 (1.463, 1.662)	0.316	0.724	< 0.001
5	2.573 (1.889, 2.843)	2.171 (1.752, 2.470)	0.193	0.535	0.003
6*	2.280 (1.989, 2.751)	1.193 (1.114, 1.316)	< 0.001	0.857	< 0.001
7*	2.790 (1.844, 2.964)	1.728 (1.588, 2.040)	0.001	0.865	< 0.001
8	1.470 (1.310, 1.808)	1.546 (1.423, 1.730)	0.529	0.916	< 0.001
9	1.781 (1.340, 2.442)	1.463 (1.376, 1.825)	0.096	0.669	< 0.001
10	2.478 (1.833, 3.209)	1.964 (1.624, 2.390)	0.116	0.705	< 0.001
11	2.326 (1.329, 2.770)	1.730 (1.586, 1.799)	0.064	0.818	< 0.001
12	2.397 (2.128, 2.675)	1.894 (1.698, 1.920)	0.058	0.642	< 0.001
13	1.913 (1.722, 2.523)	1.798 (1.528, 1.895)	0.087	0.701	< 0.001
14*	2.340 (1.598, 2.467)	1.432 (1.322, 1.546)	< 0.001	0.789	< 0.001
15	2.324 (1.818, 2.886)	1.690 (1.539, 1.933)	0.062	0.864	< 0.001
16	2.278 (1.735, 2.438)	1.837 (1.632, 2.259)	0.15	0.613	0.001
17*	1.630 (1.432, 1.944)	1.400 (1.238, 1.530)	0.003	0.769	< 0.001

* Patients with dcSSc showed increased SWV compared with healthy controls ($p < 0.05$). ** Site 1, 5: right and left middle finger (dorsum of middle phalanx); site 2, 6: right and left hand dorsum (index/middle metacarpal interspace, 2 cm proximal to the metacarpophalangeal joints); site 3, 7: right and left forearm (anterior aspect, 10 cm proximal to the ulnar styloid); site 4, 8: right and left upper arm (anterior aspect, 10 cm proximal to the medial epicondyle); site 9: forehead center; site 10: anterior chest (between sternal angle and notch); site 11: anterior abdomen (10 cm distal to the sternum); site 12, 15: right and left thigh (10 cm proximal to the patella); site 13, 16: right and left lower leg (anterolateral aspect, 10 cm proximal to the lateral malleolus); site 14, 17: right and left foot dorsum (in the first web space 2 cm proximal to the metatarsophalangeal joints). dcSSc: diffuse cutaneous systemic sclerosis; ARFI: acoustic radiation force impulse; ICC: intraclass correlation coefficient.

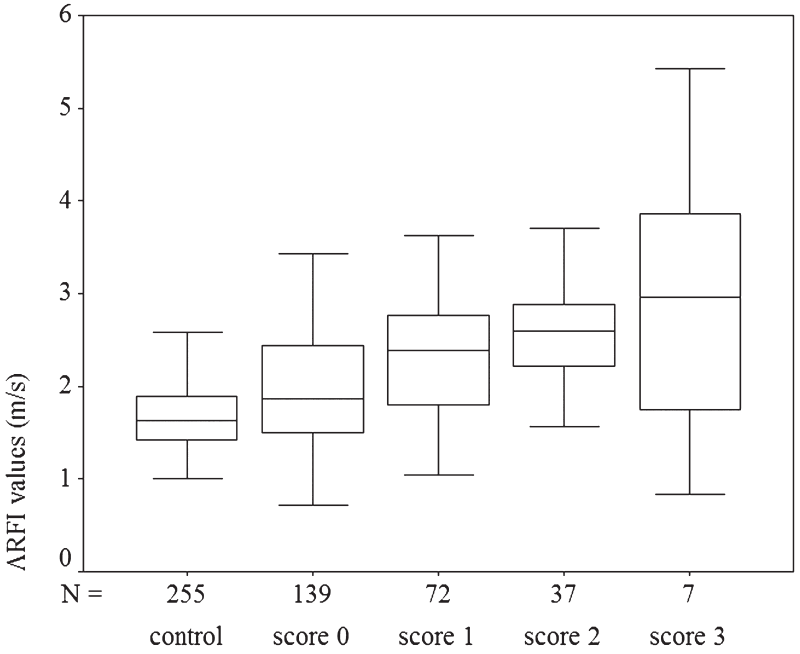

Figure 1. ARFI quantification of skin in controls and patients with systemic sclerosis; data are subdivided by clinical skin score. The SWV of scores 0, 1, and 2 were significantly higher than those of controls ($p < 0.001$, 0.001, < 0.001, respectively). Significant difference was also found between scores 0 and 1 ($p = 0.001$), and scores 0 and 2 ($p < 0.001$). No significant differences were found between mRSS 3 and 0, 1, or 2. ARFI: acoustic radiation force impulse; mRSS: modified Rodnan skin score; SWV: shear wave velocity.

was 0.9 (0.8, 1.2) mm, 1.0 (0.8, 1.2) mm, 1.2 (0.9, 1.6) mm, 1.4 (1.2, 1.8) mm, and 1.7 (1.1, 1.9) mm for controls, mRSS 0, 1, 2, and 3, respectively (Figure 2). No significant difference was found between controls and mRSS 0. The skin thicknesses of mRSS 1, 2, and 3 were significantly higher than those of controls ($p < 0.001$, < 0.001, 0.003, respectively), and significant difference existed between mRSS 0 and 1 ($p = 0.001$), and mRSS 0 and 2 ($p < 0.001$).

The sum of SWV values at 17 sites correlated with total clinical skin score ($r = 0.841$, $p < 0.001$; Figure 3). The sum of skin thickness correlated with total clinical skin score ($r = 0.740$, $p = 0.002$; Figure 4).

DISCUSSION

High-frequency and high-resolution US offer the opportunity to evaluate skin thickness and echogenicity[8]. A method of measuring skin thickness at 17 sites, corresponding to those of the mRSS, was developed by Moore, *et al*[14] using a 22-MHz probe. This scoring system may be useful for measuring small but clinically important changes over time[16]. Differences in skin thickness and echogenicity exist between patients with SSc and controls[1,17]. High-frequency US can identify the edematous phase that may precede palpable skin involvement in early SSc[3], which could be useful in identifying patients with diffuse skin involvement at a very early disease phase.

Considering that SSc is characterized by skin thickness and fibrosis, resulting in reduced dermal elasticity, and that ARFI quantification can evaluate tissue elasticity, we investigated the role of ARFI quantification in assessing skin involvement in SSc.

ARFI imaging has been applied to the liver, breast, kidney, spleen, prostate, pancreas, testes, thyroid, muscle, and tendon. The most notable use of ARFI is for assessment of diffuse liver disease, because the fibrous tissues are usually stiffer than the surrounding tissues. There is increasing evidence that ARFI can be used to diagnose liver fibrosis. A significant increase of SWV was parallel with the increase in the fibrosis stage of the liver. The major problem in the application of ARFI is that there are artifacts highly dependent on the technique such as excessive tissue motility, obesity, and cirrhosis with high tissue stiffness[15]. To our knowledge, there is little application of ARFI to skin in patients with SSc.

Our results revealed that the SWV of patients with dcSSc increased at sites 2, 3, 6, 7, 14, and 17 compared with healthy controls. The interobserver reliability of ARFI quantification was good for sites 2–4 and 6–17, suggesting that ARFI quantification could be a reliable tool in assessment of skin hardness. For sites 1 and 5 (right and middle finger), the interobserver reliability was poor (ICC 0.247, 0.535, respectively). This may be caused by the interference of bone hyperreflection and difficulties in obtaining a perpendicular image, especially in patients with bent and stiff fingers, where the probe may slide down. Iagnocco, *et al*[8] also reported that strain EUS, another kind of elasto-

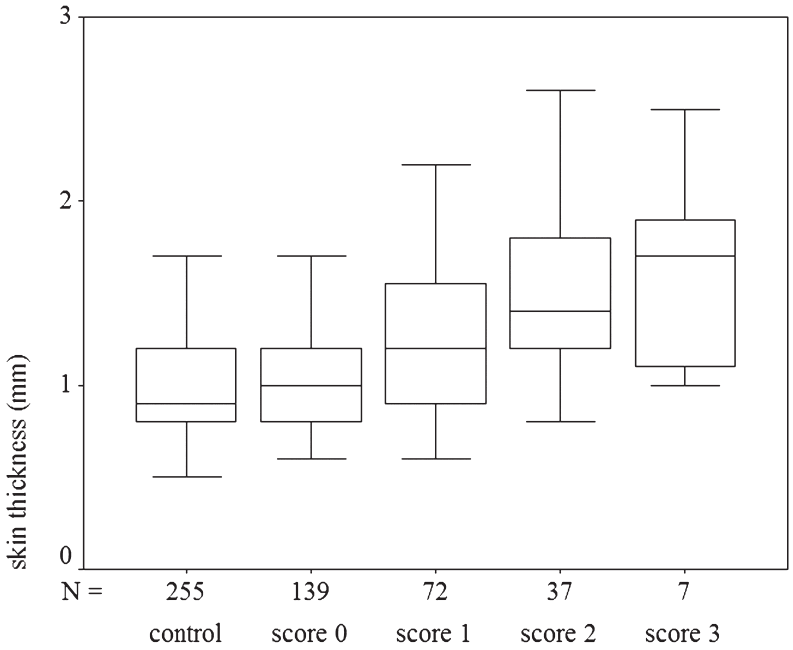

Figure 2. The thickness of skin in controls and patients with systemic sclerosis; data are subdivided by clinical skin score. The skin thickness of scores 1, 2, and 3 was significantly higher than that of controls ($p < 0.001$, < 0.001, 0.003, respectively). Significant difference was also found between scores 0 and 1 ($p = 0.001$), and scores 0 and 2 ($p < 0.001$).

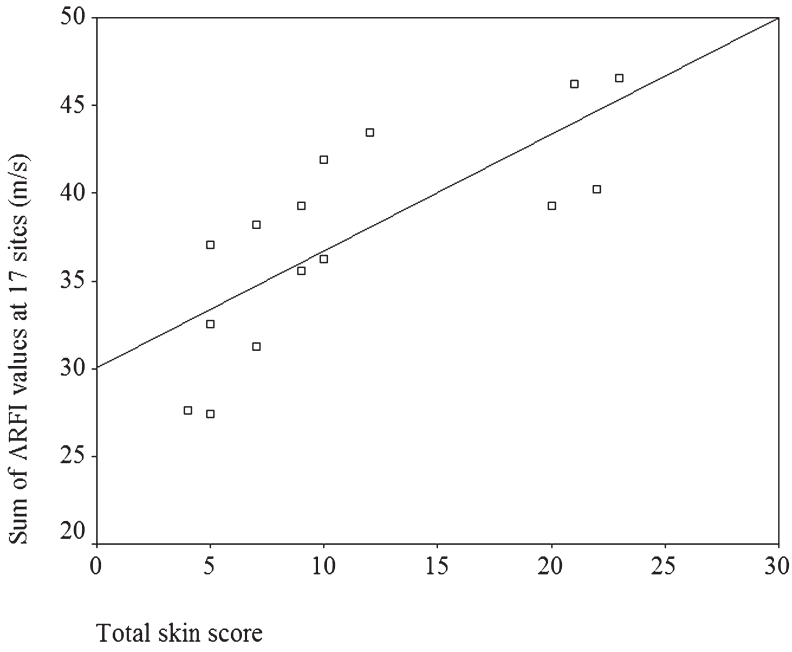

Figure 3. Comparison between the sum of SWV values at 17 sites and total clinical skin score. SWV: shear wave velocity.

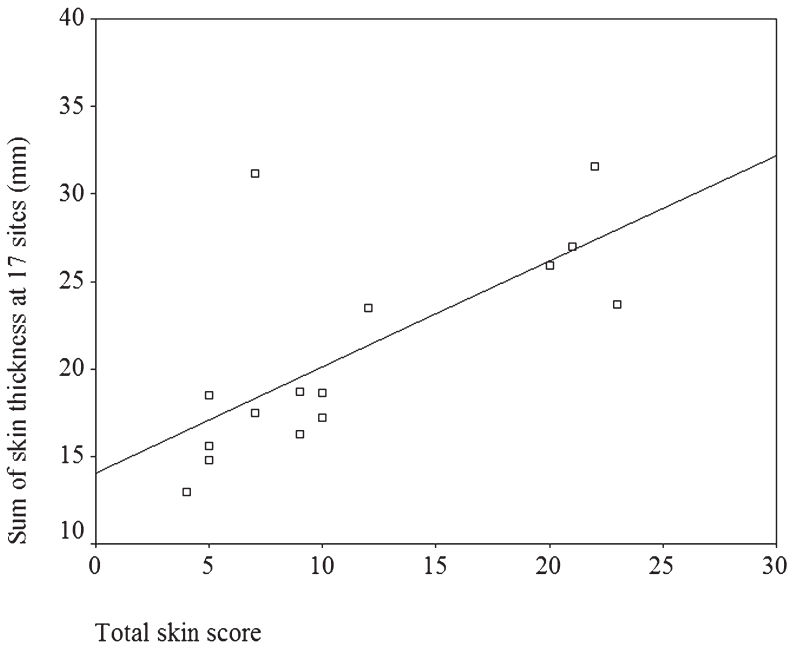

Figure 4. Comparison between the sum of skin thickness at 17 sites and total clinical skin score.

graphy US, was not useful for assessing finger involvement, where inconstant and changeable colored areas were produced owing to bone hyperreflection.

It has been shown that skin changes such as abnormal endothelial activation and procollagen production occur prior to clinical detection in patients with SSc[18]. The measured SWV of clinically uninvolved skin (mRSS = 0) in patients with dcSSc was significantly higher than that of controls, further suggesting that ARFI quantification might be a useful tool for identifying subtle skin changes that

cannot be evaluated by generally used clinical methods. Our results are in agreement with studies by Kissin, *et al*[6] that demonstrated higher durometer scores in clinically uninvolved skin compared with healthy control skin. Studies of skin biopsies, US, and durometry have shown signs of involvement of the so-called uninvolved skin, suggesting that palpation underestimates the skin fibrosis[3]. Our study suggested that ARFI quantification could identify early skin change that may precede palpable skin involvement. The SWV values increased with increasing skin scores. This could indicate that SWV values reflect skin change in patients with dcSSc; the stiffer the skin, the higher the SWV values. Although SWV values in mRSS 3 were higher than those in mRSS 0, 1, or 2, no significant difference was found between mRSS 3 and 0, 1, or 2, which may result from the relatively small number of mRSS 3 cases (n = 7), and a wider range distribution of the SWV values. The study by Nezafati, *et al*[19] compared US findings with skin histological findings and determined that US could differentiate active disease [which appeared hyperechoic (sclerosis) or isoechoic (inflammation)] from atrophy or damage (which appeared hypoechoic). And the degree of echogenicity correlated with the amount of sclerosis on histologic examination. But to date we had not found studies about the correlation between the SWV and histological findings. That would be a very interesting topic to investigate in a future study.

The skin thickness measurement with greyscale US in SSc has been studied for more than 30 years, and has been accepted as a reliable index with minimal intraobserver and interobserver variability[20]. Thus ICC was not done for US-measured skin thickness in the study. Our results were consistent with previous research in which patients with SSc had dermal thickness significantly higher than controls[1]. In our present study, the skin was thicker in patients with dcSSc compared with healthy controls at sites 1, 2, 3, 5, 6, 7, and 14. The subgroup analysis showed that no significant difference was found in skin thickness between mRSS 0 in patients with dcSSc and controls (p = 0.181). However, SWV values of clinically uninvolved skin (mRSS = 0) in patients with dcSSc were significantly higher than those of controls, suggesting that ARFI quantification is more sensitive than conventional US for detecting skin changes.

There are several limitations to our study. First, a relatively small number of patients and controls was examined. The reference values and the distribution of measured SWV in healthy controls have not yet been defined. Second, our data stem from a single center and should be confirmed by other investigators. Third, further studies are needed to evaluate the usefulness of ARFI quantification in patients' followup and clinical trials. Fourth, the measurement of mRSS is very important. Although the physician was experienced and well trained, mRSS evaluation confirmed by more clinicians might be more reliable.

We have found that ARFI quantification is feasible and reliable for assessing skin involvement in patients with dcSSc; moreover, it can identify early skin changes that may precede palpable skin involvement. ARFI quantification may be a valuable adjunct to skin evaluation in patients with SSc.

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