Quantification of skin stiffness in patients with systemic sclerosis using real-time shear wave elastography: a preliminary study

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ABSTRACT

Objective. *To assess the diagnostic value of shear wave elastography (SWE) quantification in patients with systemic sclerosis (SSc) and healthy controls.*

Methods. *Skin elastic modulus (E) values and thicknesses were measured at 6 skin sites between the SSc (n=37) and control (n=37) groups. Thickness and E values were converted into T- and E-scores, to allow skin thickness and stiffness of different regions to be quantified based on a single standard. T- and E-scores were compared with the modified Rodnan skin score (mRSS).*

Results. *E values were significantly higher in SSc patients than healthy controls at all measured sites (p<0.001), whereas skin thickness increased significantly only at fingers and forearms (p<0.001). E-score analysis revealed mRSS differences within 1.0 at most sites, while T- score evaluation only showed differences between mRSS 0 and mRSS 1 at fingers. Interestingly, mRSS correlated more closely with skin stiffness (r=0.889, p<0.001) than skin thickness (r=0.465, p=0.002).*

Conclusion. *In patients with SSc, SWE is more sensitive to detect subtle skin changes than B-mode ultrasound (US), and reflect the degree of skin involvement. As a non-invasive and operator-independent technique, SWE may provide a new and valuable method to evaluate the degree and changes of skin involvement in SSc patients.*

Introduction

Systemic sclerosis (SSc) is a heterogeneous autoimmune disorder of unknown aetiology with the hallmark of skin thickening and hardening due to excessive dermal deposition of collagen. Skin involvement can develop from oedema to extensive skin fibrosis, and eventually to atrophy. In SSc, the degree of skin involvement may associate with the severity of internal organ manifestations, poor prognosis and increased disability (1, 2). Successful clinical management of SSc requires early diagnosis and accurate evaluation of the degree of skin involvement. The modified Rodnan skin score (mRSS), which is based on palpation, is currently used by most clinicians. Advantages of the mRSS method are accessible, non-invasive, and cost-effective requires no special equipment (3-6). However, its role in evaluating sclerodermatous skin remains disputable because of its operator dependence leading to high intra- and inter-observer variability (6). Moreover, this method cannot differentiate skin thickness from tightness (2, 3, 5, 7).

The utility of B-mode ultrasound (US) to measure skin thickness in SSc has been clinically authenticated. This method can be used to estimate the extent of skin thickness, and may suggest the stage of SSc, including oedema, fibrosis, and atrophy, and may also detect subclinical dermal involvement (2, 8-13). Nevertheless, B-mode US entails two problems. First, it cannot measure skin stiffness. Second, it is challenging to accurately evaluate skin thickness when no clear boundary exists between the skin and subcutaneous tissue.

Elastography ultrasound, as newer metrics to measure tissue stiffness or elasticity, including strain elastography, acoustic radiation force impulse (ARFI, such as ACUSON S3000™ or S2000™), and shear-wave elastography (SWE, such as supersonic shear imaging), allows the assessment of skin elastic properties (8, 14-26). Among these, strain elastography has disadvantages of operator dependency, low reproducibility, and relatively qualitative evaluation (24). Both ARFI and SWE, being the latest methods, on the basis of automatic generation

and analysis of transient shear waves, possess several advantages such as real-time B-mode (2-D) imaging, operation independence, and quantitative measurements (17, 24). Compared to ARFI, SWE, thanks to its ultrafast imaging technique, can reduce the risk of artefacts due to of patients' or investigators' movements (27). The sampling gate with the minimum possible size was 2x2mm in ARFI (22), and 1mm in diameter in SWE (25, 26). Thus, it is difficult for ARFI to provide accurate skin elastic properties in those body sites with a skin thickness less than 2mm. In addition, our previous study has demonstrated that normal skin elasticity quantification by SWE has good repeatability (intra- and inter-class correlation coefficient >0.85) (25). Meanwhile, some studies (23, 26) showed that both ARFI and SWE could successfully differentiate sclerotic lesions of morphea from normal dermis, but SWE provided better differentiation and less variability than ARFI.

To our knowledge, fewer studies on the value of SWE-measured skin stiffness in patients with SSc have been so far conducted. We therefore assess skin thickness and stiffness at 6 sites (bilateral fingers and forearms, chest and abdominal walls) in patients with SSc. In this study, skin thickness and stiffness were expressed as relative values (T- and E-scores) compared to average values for healthy controls, to allow skin abnormalities to be assessed for different sites of the body. The degree of overall skin involvement was then evaluated by adding up the T- and E-scores for the 6 body sites.

Methods

Patients with SSc and healthy controls

This study was approved by the Ethics Committee of West China Hospital, Sichuan University (approval number: ChiCTR-DCD-15006851), and performed in accordance with the Helsinki Declaration of 2013. All participants provided written informed consent for the scientific acquisition and analysis of their imaging data at the time of examination. A total of 37 patients with SSc, all fulfilling the American College of Rheumatology criteria for the classification of SSc (28) and early SSc (29), alongside 37 healthy controls, matched with age, sex and body mass index (BMI), were prospectively included in this study.

The 37 patients were consecutively recruited at the Dermatology Department of West China Hospital, Sichuan University, from September 2015 to April 2017. Initially, all the patients with SSc underwent clinical and serological assessments. An experienced dermatologist, trained at the European League Against Rheumatism Scleroderma Trials and Research group course, performed the mRSS over 17 anatomical sites (13) in each patient, and was unaware of B-mode US or SWE assessment results. Measurements of mRSS were carried out only once for each subject.

Meanwhile, 37 healthy controls (medical students, nurses, and doctors from our hospital, juveniles under 18 years old from doctor's children) fulfilled the following criteria: no pregnancy, no scar at the measurement site; no history of skin, rheumatoid immune, metabolic or endocrine diseases, no previous radiotherapy or chemotherapy. No additional tests were performed for the control group.

The following parameters were recorded for each participant: age, sex, weight, height, and BMI. To assess the effect of age and obesity, the associations of skin E-scores with age and BMI were examined for control subjects.

Ultrasonography (B-mode US and SWE)

The participants were instructed not to perform any form of exercise 2h prior to examination, and rest completely for 5 min before examination. Six skin sites were examined in each participant according to the previous studies (13, 25): sites 1 and 3, right and left middle fingers (dorsum of the middle phalanx); sites 2 and 4, right and left forearms (anterior aspect, 10 cm proximal to the ulnar styloid); site 5, anterior chest (between the sternal angle and sternal notch); site 6, anterior abdomen (10 cm distal to the sternum). Sites 1, 2, 3, and 4 were assessed with the volunteer putting the hands and arms on the examination bed, with palms down in a naturally flexed state without strength. Sites 5 and 6 were examined with the volunteer in the supine position with both hands on the waist and shoulders relaxed. Each subject was asked to stop breathing for a moment to minimise breathing motion. Room temperature was controlled at 25°C.

B-mode US examination was performed by an experienced sonographer in musculoskeletal ultrasonography on an Aixplorer US system (SuperSonic Imagine, Aix-en-Provence, France) with a SL 15–4 multi-frequency linear probe operating at 4–15MHz. The superficial musculoskeletal setting was selected with the default mode of instrument "standard". The transducer tip was covered with several millimeters of ultrasound gel and placed perpendicularly to the skin smoothly in a longitudinal section to enable total contact causing no pressure on the skin. B-mode US was used to measure skin thickness (epidermis and dermis) at the above six sites. Skin thickness was measured three times for the same location; average value was expressed in millimeters (mm).

After shifting to the SWE mode, ROIs (region of interest) for recording E value were set at the same site as in B-mode US. The operators adopted the default SWE ROI size, and manipulated the ROI to include the area from gel to the subcutaneous tissue. At each site, the transducer was held for around 10 seconds until stable colour was obtained in the SWE ROI (coloured square), and the image was then saved. The degree of downward adjustment of scale varied, ranging from 800 to 50 kPa as needed so that some skin areas appeared orange or red. A round Q-box (a small circle of diameter 1~2 mm in our study) adjusted to skin thickness, was placed in the red or orange skin area on the colour-coding SWE image. The system automatically calculates a set of the elastic moduli, including the mean, maximum, minimum, and SD for E values within Q-box in kPa (kilopascal) and displays on the screen (Fig. 1). Mean kPa was selected as representative value for each image and defined here as "E-values". For each skin site, three consecutive skin E

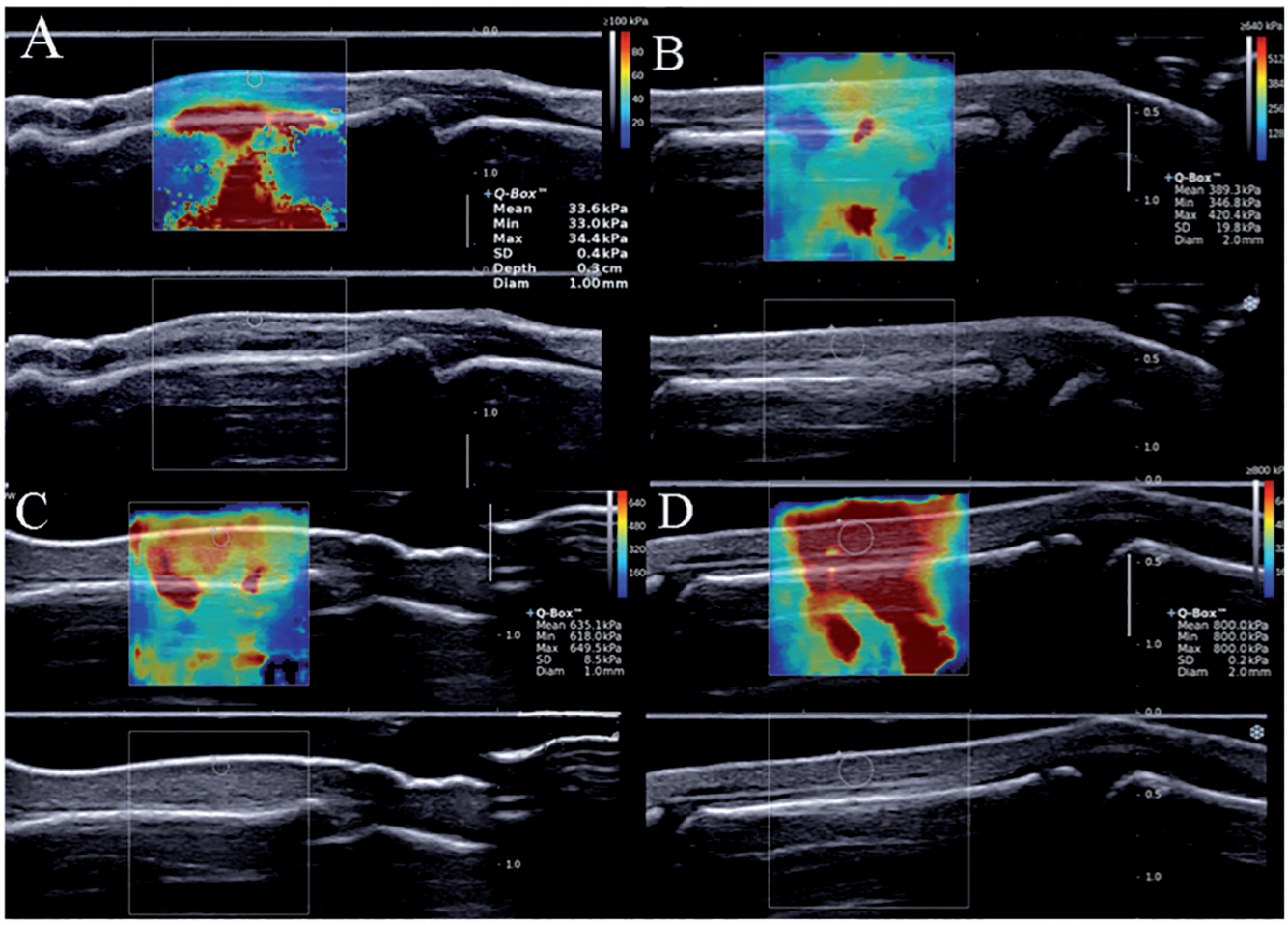

Fig. 1. Representative SWE (top frame) and B-mode US (bottom frame) images of the skin at finger in healthy controls (**A**) and patients with SSc (**B-D**). On every SWE image (top frame), a colour map of relative skin elasticity (stiffness) is shown in the SWE ROI (coloured square). In the SWE colour coded image (top frame), skin of patients with SSc mainly appeared orange or red with range > 200kPa, uneven or not; meanwhile, healthy controls showed uniform blue or blue-green colour with range of 100 kPa.

value measurements (one Q-box measurement per image) were obtained with similar scanning views. From the three measurements, average E value was assessed; the results were expressed in kilopascals (kPa).

T-score thickness, E-score stiffness, total T-score thickness, total E-score stiffness

To compare skin abnormalities at the various sites, it is necessary to standardise the measurement values because the original skin stiffness and thickness vary at the different body sites. Therefore, skin thickness and E values were converted into T- and E-scores by the following formulas:

$X\text{-}score_i = [X_{SSc}\text{-}\bar{X}_{hc}] / SD\ (X_{hc})$

Where X_{SSc} represents the skin thickness or elastic modulus measured at a given skin site of SSc patient *i*, $\bar{X}_{hc}$ and $SD\ (X_{hc})$ represents the mean and standard deviation of the skin thickness or elastic modulus measured at that skin site of healthy controls. That is, the T- and E-scores represent the standardised degrees of deviation from normal control averages. The sum of T- and E-scores for all 6 body sites were defined as total T-score thickness and E-score stiffness, respectively, and used to evaluate the association with modified Rodnan total skin scores (mRTSS) for all 17 body sites.

Statistical analysis

The statistical analysis was performed with SPSS v. 21.0 (SPSS, Chicago, Ill, USA).

The normality of continuous variables in participants was tested by the Kolmogorov-Smirnov test and Q-Q plot. Unpaired Student's *t*-test was used to compare skin thickness and stiffness between patients and controls in various sites. To assess the associations of age and obesity with skin stiffness in controls, we applied Pearson correlation analysis. Among subgroups with different mRSS values, skin E- and T-scores were compared using one way analysis of variance (ANOVA) according to data distribution feature. The Pearson correlation coefficient (r) was employed to determine the associations of mRTSS with total T- and E-scores. Two sided *p*-values below 0.05 were considered statistically significant.

Results

Characteristics of healthy controls and SSc patients

Table I summarises the main clinical features of 74 participants. Sex ratio was the same for SSc and control groups.

Table I. Clinical features of SSc patients and healthy controls.

	SSc patients (n=37) (range)	Healthy controls (n=37)	*p*-value
Age (y)	42.0±14.6 (12-72)	43.1±15.3 (12-78)	0.656
Gender, female: male	32:5	32:5	
BMI (kg/m^2)	21.3±3.4 (18.9-23.8)	21.5±3.1 (17.4-23.4)	0.742
mRTSS	23.0±11.3 (7-46)		
ANA (±)	30/7		
SCL-70 (±)	15/22		
Limited/Diffused	14/23		
Disease duration	4.8±4.4 (10m-16y)		

SSc: systemic sclerosis; BMI: body mass index; ANA: antinuclear antibodies; mRTSS: modified Rodnan total skin score; SCL-70: Anti-topoisomerase-I antibodies; m: month; y: year.

Table II. B-mode US-measured skin thickness and SWE-measured skin E values at bilateral fingers and forearms in healthy controls.

	Right	Left	*p*-value
Skin thickness (mm)			
Finger	1.06 ± 0.13	1.06 ± 0.14	0.841
Forearm	1.40 ± 0.20	1.41 ± 0.19	0.823
Skin E values(kPa)			
Finger	32.31 ± 10.45	32.06 ± 9.50	0.384
Forearm	14.51 ± 5.69	13.78 ± 4.07	0.443

US: ultrasound; SWE: shear wave elastography; mm: millimeter; kPa: kilopascal.

Age and BMI were similar (p=0.656 and 0.742, respectively) between the two groups. Meanwhile, mRTSS was 23.0±11.3 (range 7-46) for the SSc patients. And the SSc group consisted of 23 diffused subsets and 14 limited subsets. Results of antinuclear antibodies and anti-topoisomerase-I antibodies tests were also given in the table.

Skin thickness and stiffness in healthy controls and SSc patients

The differences of B-mode US-measured skin thickness and SWE-measured skin E values were statistically insignificant in healthy controls between right and left fingers, and between right and left forearms, as shown in Table II. Figures 2A and 2B show the associations of total E-score stiffness with age and BMI in controls, respectively. No significant association was observed of total E-score stiffness with either age (r=-0.104, p=0.541) or BMI (r=-0.215, p=0.201). Figure 2C shows skin E values for each body site in controls. A wide variation in skin elastic modulus values was observed, especially for dorsal fingers.

B-mode US-measured skin thickness values in patients with SSc were increased significantly at fingers and forearms compared with those obtained for healthy controls, whereas SWE-measured skin E values in patients with SSc were increased significantly at all sites (Table III).

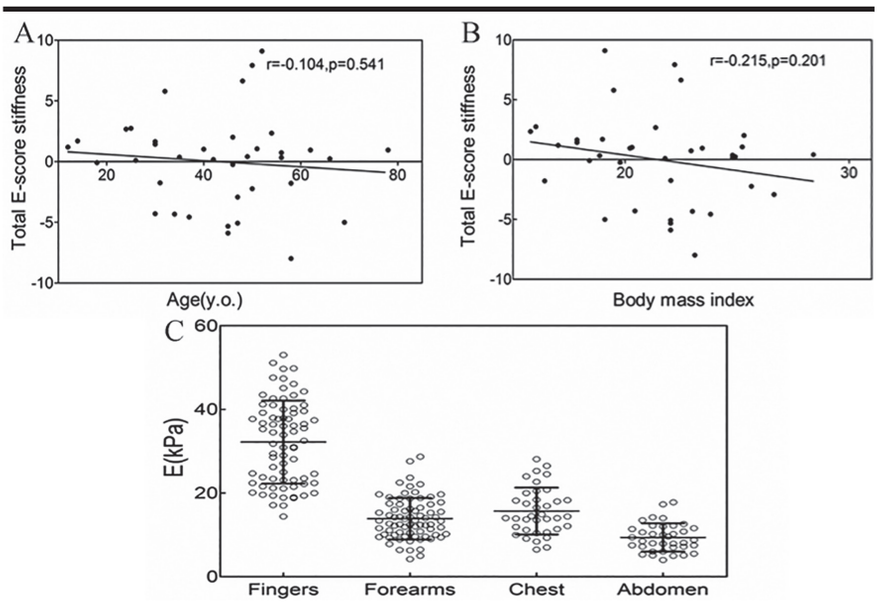

Fig. 2. Skin stiffness in healthy controls. (**A**) Pearson correlation analysis between total E-score stiffness and age. (**B**) Pearson correlation analysis between total E-score stiffness and BMI. (**C**) Skin E values at each body site. Small white circles indicate E values (n=74 for fingers and forearms; n=37 for chest and abdomen). Fine and thick lines indicate means ± S.D. of skin E values.

Skin scores

Figures 3A and 3B show the skin thickness T-scores and skin stiffness E-scores determined by mRSS for all body sites in SSc patients and healthy controls. The mean skin thickness T-scores for mRSS 0 (278 measurement sites), 1 (54), 2 (62) and 3 (50) were -0.12, 0.45, 1.61 and 4.55, respectively. The differences among them were generally statistically significant (p<0.05) regardless the insignificant difference between mRSS 1 value and mRSS 0 or 2 values. The mean skin stiffness E-scores for mRSS 0 (278 measurement sites), 1 (54), 2 (62) and 3 (50) were 0.43, 5.36, 15.65 and 40.75. The differences among these values were also statistically significant (all p<0.05). However, the values showed a wide distribution, especially for the group with mRSS 3. The mean T-score thickness and E-score stiffness at four body sites (fingers, forearms, chest, and abdomen) are shown in Figure 3C and 3D. The E score stiffness for the four skin scores were significantly difference at all four body sites, with the fingers and forearms being the most significant, possibly because the skin involvement is more common in SSc at these two sites. The mean T-scores for the four skin scores were only signifi-

Table III. The difference of B-mode US-measured skin thickness and SWE-measured skin elastic modulus between patients with SSc and controls at different body sites.

	SSc Patients (95%CI) (n=37)	Healthy controls (95%CI) (n=37)	*p*-value
Skin thickness(mm)			
***Finger(bilateral)	**1.68**±0.42(1.58-1.78)	**1.06**±0.14(1.03-1.09)	<0.001
***Forearm(bilateral)	**1.52**±0.26(1.46-1.58)	**1.41**±0.20(1.36-1.45)	<0.001
Chest wall	**1.78**±0.34(1.67-1.90)	**1.80**±0.24(1.72-1.88)	0.757
Abdominal wall	**1.85**±0.37(1.73-1.98)	**1.93**±0.20(1.87-2.0)	0.243
Skin elastic modulus (kPa)			
***Finger(bilateral)	**351.66**±236.33(296.91-406.41)	**32.19**±9.92(29.89-34.49)	<0.001
***Forearm(bilateral)	**52.89**±43.22(42.87-62.90)	**13.89**±4.95(12.74-15.04)	<0.001
***Chest wall	**53.52**±47.75(37.60-69.45)	**15.70**±5.61(13.83-17.57)	<0.001
***Abdominal wall	**27.76**±32.95(16.77-38.75)	**9.38**±3.39(8.25-10.51)	<0.001

***indicates $p<0.001$.
US: ultrasound; SWE: shear wave elastography; SSc: systemic sclerosis; CI: confidence interval; mm: millimeter; kPa: kilopascal.

cantly different at fingers and forearms when mRSS differs 2 or above.

Correlation of skin scores

Correlations of mRTSS with total T-scores for thickness and total E-scores for stiffness are shown in Figures 4A and 4B. Interestingly, mRTSS correlated more closely with E-score stiffness by SWE (r=0.889, $p<0.001$) than T-score thickness by B-mode US (r=0.465, $p=0.004$).

Discussion

Skin thickening and tightness is main characteristic manifestations of SSc, and the degree of skin involvement associates with the severity of internal organ manifestation(s), poor prognosis, increased disability and shorter life expectancies. Thus, most cases require the quantitative assessment of skin involvement of SSc. B-mode US is cost-effective, non-invasive, and accessible, and multiple studies demonstrated that it could assess SSc skin thickness and echogenicity changes quantitatively, reliably and reproductively (2, 8-13).

SSc leads to skin stiffness as well, and elastography ultrasound has been proven effective in detecting tissue mechanical elasticity; meanwhile, recent studies indicated elastography ultrasound could evaluate skin elasticity quantitatively and reproductively (8, 14-26), and these values were also well correlated with the clinical skin

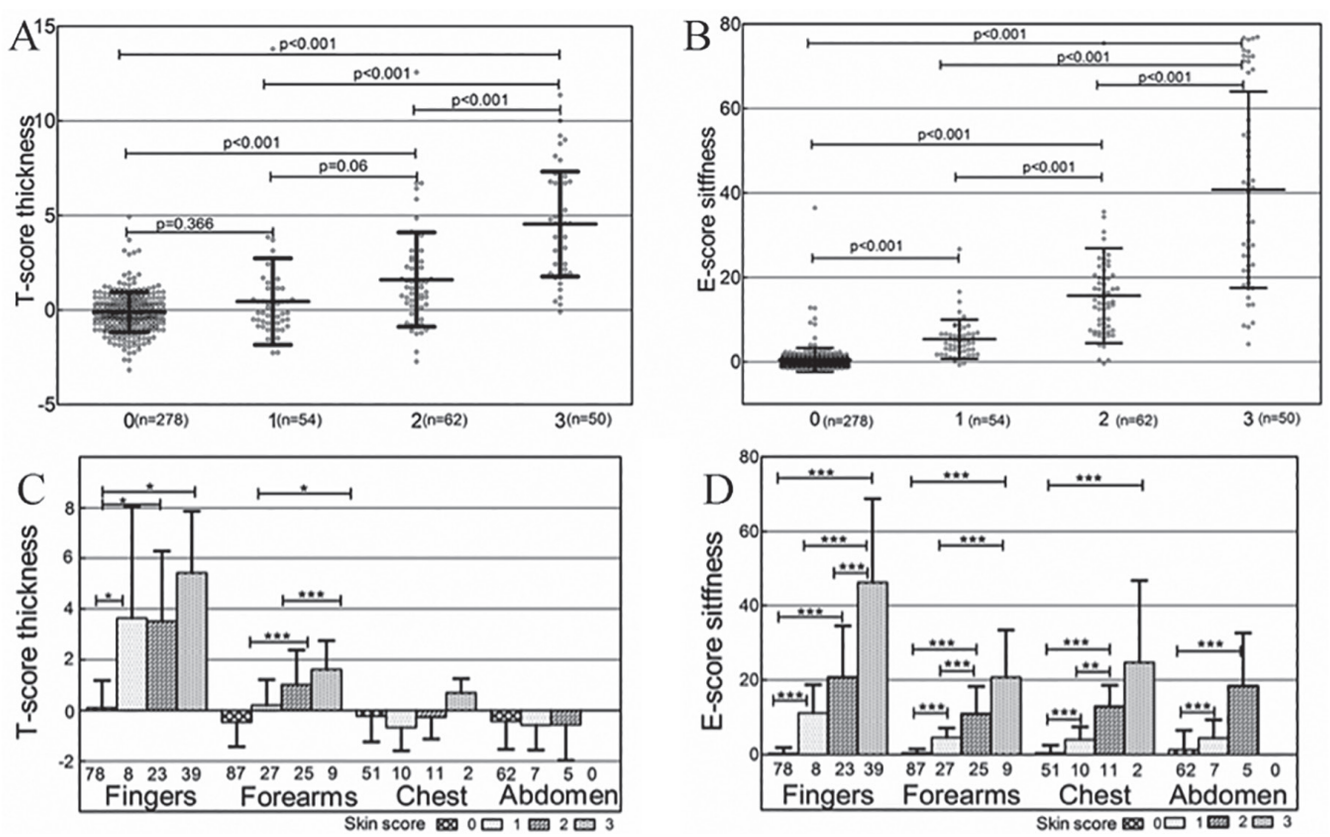

Fig. 3. Relationship between modified Rodnan skin score (mRSS) and T-score thickness or E-score stiffness. T-score thickness (**A**) and E-score (**B**) stiffness are subdivided by the clinical skin score (0-1-2-3) regardless of the body site. Note that the right and left fingers or the right and left forearms are counted as "fingers" or "forearms". Numbers in parentheses below skin scores indicate the total numbers of sites measured (The mRSS values of the controls were set to 0). T-score thickness (**C**) and E-score stiffness (**D**) are plotted for bilateral fingers, bilateral forearms chest wall and abdominal wall. The scores are subdivided by clinical skin score (mRSS 0-3; the values of the controls were set to 0). The number below the bars indicates the number of values associated with the given mRSS at different skin sites.*$p<0.05$, **$p<0.01$, ***$p<0.001$.

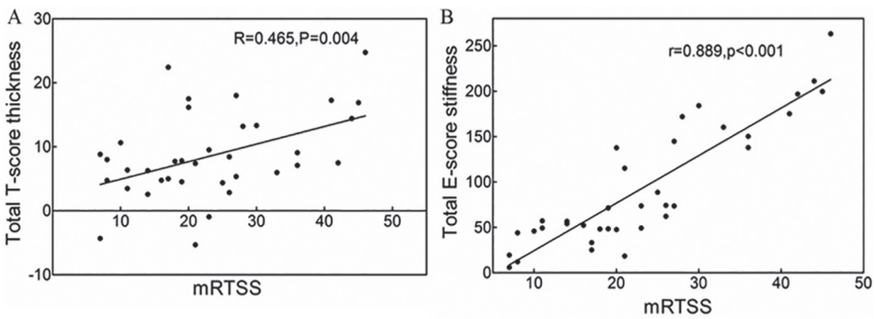

Fig. 4. Relationship between mRTSS and total T-score thickness (**A**) or total E-score stiffness (**B**). Total T-score thickness and total E-score stiffness represents the sum of T- or E-scores at 6 body sites, respectively. mRTSS: modified Rodnan total skin score.

score, mRSS (8, 17, 22). It can potentially document disease manifestations in deep internal organs in SSc patients with multimodal ultrasound imaging techniques, such as the colour Doppler imaging (CDI), the harmonic tissue imaging (THI), and contrast enhanced ultrasound (CEUS) imaging for most of the tissues and blood vessels (30-32). We therefore explored the potential role of SWE quantification in assessing the degree of skin involvement in SSc.

Our study showed that skin E values in patients with SSc increased significantly at all examined sites compared with healthy controls, whereas skin thickness increased only at fingers and forearms (Table III). These results suggest that measurements of E-values could be more reliable and sensitive than skin thickness to assess skin involvement in SSc. Our results corroborate well with those of previous studies (2, 8-13), showing that the dermal thickness was significantly higher in patients with SSc than in controls, and B-mode US is a reliable tool for the detection of skin thickening in SSc. The results of skin stiffness measurement are partly in agreement with those of Santiago *et al*. (22), *e.g*. a significant increased stiffness at bilateral fingers and forearms in SSc patients over controls. Contrary to our findings, they did not observe the difference in stiffness between the SSc and the healthy controls at the chest wall and the abdominal wall. Using the same imaging technique (ARFI, Siemens Acuson) as Santiago *et al*. (22), Hou *et al*. (17) observed an significant increase of skin stiffness at bilateral forearms ($p<0.05$), but not at bilateral fingers, chest and abdominal walls in SSc patients as compared to the controls. The above discrepancies of skin stiffness results could be related to the extent of skin involvement of study patient populations, being highly heterogeneous in part, probably also related to the difference in SSc subtypes, sample size, and methods of measurements used in each study. For example, according to the extent of skin involvement, SSc can be classified into two main clinical subsets: the limited subset and diffused subset (29). In Santiago's study, half of the patients (13/26) present diffused cutaneous SSc, while our patients consist mainly of diffused subset (23/37), and all of the patients are diffused subset in Hou's report (15/15). Besides differences in SSc subtypes and sample size, Hou (17) and Santiago *et al*. (22) used another US elastography imaging technique (ARFI) for the assessment of skin stiffness. The imaging technology (ARFI *vs*. SWE) may also be a potential cause of the different results.

The standardisation procedure adopted here uses T- and E-scores so that skin thickness and stiffness of different regions can be quantified based on a single standard, because skin thickness and stiffness (Fig. 2C) vary among the different regions assessed (13, 24, 33). Furthermore, we could calculate the degree of total skin involvement in a patient based on T-score thickness, the sum of T-scores, E-score stiffness, the sum of E-scores at the 6 body sites.

As shown in Figure 3B, mean skin E-score stiffness increased significantly for all 74 participants with mRSS. These findings suggest that SWE can identify mRodnan skin score differences. Nevertheless, Figure 3A showed that the mean skin T-score stiffness increased insignificantly for the 74 participants between mRSS 1 and mRSS 0 or mRSS 2. As shown in Figure 3C, when the mRSS differences differs 2 or above, the T-scores were statistically significant only at fingers and forearms. While the differences among T-scores were not statistically significant at the chest and abdominal walls. We could not determine whether this is due to insufficient data or potential B-mode US limitations. However, as seen in Figure 3D, the differences within 1.0 between E-scores were statistically significant at most sites. In other words, the E-score, representing skin stiffness obtained by SWE, seems correlate much better with the clinical skin score than T-score (skin thickness), whether for all skin sites (Fig. 3B *vs*. Fig. 3A) or for an individual skin site (Fig. 3D *vs*. Fig. 3C). This observation is further confirmed by Figure 4, where the total T-score (A) and the total E-score (B) are plotted with the modified Rodnan total skin score (mRTSS) measured on 17 skin sites in SSc patients. A better correlation can be found between the mRTSS with the total E-values ($r=0.889$, $p<0.001$) than with the total T-score (($r=0.465$, $p=0.004$).

These results suggest that SWE may be used to quantitatively characterise the degree of skin involvement in SSc, and the skin stiffness seems to be a parameter more robust and sensitive than the thickness to detect subtle changes of skin involvement in SSc. Hou *et al*. (17) also showed that the total SWV (shear wave velocity) values correlated better with the sum of the mRSS over 17 skin sites ($r=0.841$, $p<0.001$) than those of the skin thickness ($r=0.740$, $p=0.002$). Santiago *et al*. (22) studied the correlation of local mRSS and shear wave velocity in 17 sites and showed correlation coefficients were 0.525-0.748 for forearm right and left, hand left, phalanx right and left and thigh right and left. We speculate that it may not be necessary to perform SWE examination for 17 sites in patients with SSc, and data from 6 sites may reflect the severity of skin involvement. Further investigation of SWE assessment in 17

sites and more optimised site combination is necessary.

In this study, no significant correlation was obtained between skin stiffness (total E-score stiffness) and either age or BMI in healthy controls. Sex differences in skin stiffness could not be clarified in this study because data for male subjects were insufficient. Further study will be required to examine sex differences in skin properties for healthy control subjects as well.

Kaloudi *et al*. (12) reported that skin thickness was different in various disease phases (oedematous, fibrotic or atrophic). Wang *et al*. (26) showed that SWE combined with the measurement of skin thickness was able to quantitatively assess and monitor localised scleroderma (LS) disease severity and progression. Unfortunately, no patients in the atrophy phase, and only 2 with oedema were included in the present study. Hence, inclusion of patients of different clinical phases in a larger study population would be crucial to confirm whether SWE-measured skin stiffness could differentiate among disease phases.

Kuwahara *et al*. (4) demonstrated that the mRTSS positively correlates with functional disability scores. Therefore, further studies should determine whether total E-score stiffness correlates with functional indices such as the classical HAQ-disability index, scleroderma-visual analogue scale and UK Scleroderma Functional Score. Rodnan *et al*. (34) demonstrated that skin score correlates with the weight of a skin punch biopsy. Further investigation is needed to assess whether skin stiffness represents a histological characteristic, such as pathological staining of collagen and fiber.

Our study had some limitations that should be pointed out. First, the sample size of SSc was still relatively small (n=37) due to the low prevalence of the disease. Second, the transducer frequency is relatively low (<15 MHz), so that it is difficult to precisely and separately measure the epidermis and dermis. Finally, we only examined 6 of 17 sites by SWE instead of 17 sites on the basis of mRSS.

In conclusion, SWE is more sensitive in detecting skin changes than B-mode US, reflecting the degree of skin involvement in patients with SSc. SWE quantification may provide a new and valuable tool to evaluate skin changes in patients with SSc.

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