The impact of transducer frequency in ultrasound evaluation of subclinical skin involvement in limited cutaneous systemic sclerosis patients

Sirs,

Systemic sclerosis (SSc) is a connective tissue disease, characterised by progressive fibrosis of internal organs and skin (1). Although the modified Rodnan skin score (mRSS) measures skin involvement, its limitations include its inability to detect small but clinically relevant changes in skin thickness over time (2). It has recently been demonstrated that skin high frequency ultrasound (US) can identify subclinical dermal involvement, even in skin areas with normal mRSS (=0) (3, 4).

In this new work, the dermal thickness (DT), assessed by 18 and 22 MHz probes, in limited cutaneous systemic sclerosis (lcSSc) patients was compared to healthy subjects.

Written informed consent and local ethical board approval was obtained for 48 patients (pts) with lcSSc (inclusion criterion) (1, 2, 5), (40 females and 8 males, average age 62±13SD, average disease duration 5±5SD years) and a control group (48 sex/age matched healthy subjects (CNT), all subjects were Caucasian. All the lcSSc patients met either the 2013 ACR/EULAR SSc criteria (39 pts), or the LeRoy's criteria for the classification of early SSc (9 pts) (5, 6). Thirty-three lcSSc patients had an antinuclear antibody profile that included anticentromere antibodies, 9 speckled and nucleolar, 6 speckled; regarding ENA profile: 9 patients had positive anti-Scl-70, 1 had anti-RNA polymerase III and 5 were ENA-negative. Any patients with a health condition (*e.g.* presence of lower extremity oedema) that might have confounded the DT evaluation were excluded. The DT in the 17 skin areas routinely evaluated by mRSS were assessed in all cases by both an 18 and a 22 MHz US probe (MyLab 25, Esaote, Genoa, Italy) (3). The intra-operator reliability was calculated by the same operator performing the US twice for each probe. DT was measured on two different days to ensure the second reading was independent from the first. Nailfold videocapillaroscopy (NVC) (Videocap, DS Medica, Milan, Italy) defined the appropriate microangiopathy NVC pattern: 16 pts for each pattern ("Early", "Active" and "Late") (7, 8).

Non-parametric tests processed the data, Intraclass Correlation Coefficient (ICC) assessed the Intra-operator repeatability and the any p-value lower than 0.05 was considered statistically significant. The results are reported as means with standard deviation (SD), median and interquartile range (IQR). The DT for the 22 MHz probe had statistically significantly higher DT than the 18 MHz probe in all body areas in lcSSc patients and controls (Table I). The 22 MHz probe showed that lcSSc patients had significantly higher median DT than controls in all six clinically unaffected skin areas ($p<0.01$) on the basis of a normal mRSS (=0), in line with their lcSSc diagnosis, whilst the 18MHz probe identified only 4/6 skin areas (both arms, chest and abdomen) (3).

There was a positive statistically significant correlation between the two probes in the DT evaluation ($p<0.0001$, r=0.92) and between both probes and mRSS ($p<0.0001$ for both, r=0.50 for the 18 MHz transducer and r=0.58 for the 22 MHz probe). The DT in lcSSc patients worsened as did the microangiopathy pattern (Early, Active and Late) ($p<0.02$, r=0.88).

The time needed to perform each of the three methods to assess DT was 26±3, 19±2 and 10±2 minutes, for the 18 and 22 MHz transducers and mRSS (respectively $p<0.0001$).

The 18 MHz probe had an intra-operator reproducibility of 96% (95%CI 0.92 to 0.98), and the 22 MHz probe 98% (95%CI 0.97 to 0.98), the mRSS was 95% (95%CI 0.94 to 0.98).

We believe that lower frequency may provide an underestimation of DT. We confirm that high frequency US with a 22 MHz probe not only offers better resolution and visualisation of derma and a more accurate DT determination and qualitative skin assessment (9, 10), but may also reduce the intra-operator variability and time required for DT measurement compared to an 18 MHz probe. These data imply high frequency US plays an important role in the detection of subclinical changes in lcSSc. Further studies are ongoing.

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Table I. Dermal thickness (DT) in healthy subjects (CNT) and in limited cutaneous systemic sclerosis (lcSSc) patients.

Skin area	lcSSc			CNT			lcSSc *vs.* CNT	
	18 MHz Median DT [IQR]	22 MHz Median DT [IQR]	*p*-value 18 *vs.* 22 MHz	18 MHz Median DT [IQR]	22 MHz Median DT [IQR]	18 *vs.* 22 18 *vs.* 22 MHz	*p*-value 18 MHz	*p*-value 22 MHz
Chees	0.88 [0.16]	0.90 [0.17]	<0.0001	0.68 [0.05]	0.69 [0.06]	0.001	<0.0001	<0.0001
3rd right finger	0.88 [0.27]	1.32 [0.55]	<0.0001	0.69 [0.10]	0.7 [0.10]	<0.0001	<0.0001	<0.0001
3rd left finger	0.93 [0.21]	1.32 [0.60]	<0.0001	0.70 [0.10]	0.71 [0.10]	<0.0001	<0.0001	<0.0001
Right hand dorsum	0.85 [0.23]	0.97 [0.33]	<0.0001	0.68 [0.09]	0.70 [0.08]	0.008	<0.0001	<0.0001
Left hand dorsum	0.85 [0.23]	0.97 [0.33]	<0.0001	0.69 [0.08]	0.70 [0.07]	0.003	<0.0001	<0.0001
Right forearm	1.00 [0.29]	1.10 [0.43]	<0.0001	0.76 [0.07]	0.77 [0.08]	0.003	<0.0001	<0.0001
Left forearm	1.00 [0.34]	1.05 [0.44]	<0.0001	0.76 [0.07]	0.77 [0.09]	0.003	<0.0001	<0.0001
Right upper-arm	1.10 [0.22]	1.20 [0.31]	<0.0001	0.85 [0.12]	0.86 [0.12]	0.008	<0.0001	<0.0001
Left upper-arm	1.10 [0.20]	1.15 [0.30]	<0.0001	0.85 [0.10]	0.86 [0.12]	0.005	<0.0001	<0.0001
Chest	1.30 [0.30]	1.31 [0.20]	<0.0001	1.12 [0.02]	1.13 [0.09]	0.001	0.005	<0.0001
Abdomen	1.30 [0.20]	1.40 [0.30]	<0.0001	1.12 [0.02]	1.13 [0.05]	0.009	0.005	<0.0001
Right thigh	1.30 [0.41]	1.40 [0.30]	<0.0001	1.07 [0.34]	1.10 [0.34]	0.003	0.1	0.005
Left thigh	1.20 [0.40]	1.40 [0.35]	<0.0001	1.09 [0.34]	1.10 [0.34]	0.006	0.1	0.005
Right leg	1.00 [0.26]	1.10 [0.29]	<0.0001	0.93 [0.03]	0.94 [0.04]	0.004	0.01	0.005
Left leg	1.09 [0.29]	1.10 [0.36]	<0.0001	0.93 [0.03]	0.89 [0.04]	0.005	0.01	0.004
Right foot	0.98 [0.11]	0.99 [0.80]	<0.0001	0.86 [0.03]	0.89 [0.04]	0.009	<0.0001	<0.0001
Left foot	0.98 [0.20]	0.99 [0.22]	<0.0001	0.89 [0.04]	0.90 [0.04]	0.004	<0.0001	<0.0001

Dermal thickness (DT) in healthy subjects (CNT) and in limited cutaneous systemic sclerosis (lcSSc) patients, evaluated by both 18 and 22 MHz probes in the 17 skin areas. DT evaluated by the 22 MHz probe was significantly higher in all body areas compared to those identified by the 18 MHz probe, both in lcSSc patients and in CNT (the DT ultrasound values were recorded in millimetres).

Letters to the Editors

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References

1. KRIEG T, TAKEHARA K: Skin disease: a cardinal feature of systemic sclerosis. *Rheumatology* 2009; 48: iii14-18.
2. KALDAS M, KHANNA PP, FURST DE *et al.*: Sensitivity to change of the modified Rodnan skin score in diffuse systemic sclerosis-assessment of individual body sites in two large randomized controlled trials. *Rheumatology* 2009;48:1143-46.
3. 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: 61.
4. 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: 181.
5. LEROY EC, MEEDSGER TA JR: Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001; 28: 1573-76.
6. VAN DEN HOOGEN F, KHANNA D, FRANSEN J *et al.*: 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2013; 72: 1747-55.
7. CUTOLO M, SULLI A, PIZZORNI C, ACCARDO S: Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. *J Rheumatol* 2000; 27: 155-60.
8. SULLI A, SECCHI ME, PIZZORNI C, CUTOLO M: Scoring the nailfold microvascular changes during the capillaroscopic analysis in systemic sclerosis patients. *Ann Rheum Dis* 2008; 67: 885-87.
9. SANTIAGO T, SANTIAGO M, RUARO B, SALVADOR MJ, CUTOLO M, DA SILVA JAP: Ultrasonography for the assessment of skin in systemic sclerosis: a systematic review. *Arthritis Care Res* (Hoboken) 2019; 71: 563-74. May 21.
10. SCHEJA A, AKESSON A: Comparison of high frequency (20 MHz) ultrasound and palpation for the assessment of skin involvement in systemic sclerosis (scleroderma). *Clin Exp Rheumatol* 1997; 15: 283-8.