White Paper

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Measuring skin thickness of systemic sclerosis patients

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Preliminary study show that elastosonography improves ultrasound's reliability to measure skin thickness of systemic sclerosis patients helping the identification of dermis-hypodermis interface

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Systemic sclerosis (SSc) is a systemic connective tissue disease and its skin's involvement is a disabling feature closely linked with organ involvement and increased mortality[1-4]. The semi-quantitative modified Rodnan skin score (mRSS) method is currently the most widely used technique to assess SSc patients' skin thickness. This method evaluates 17 skin areas through clinical palpation using a 0-3 scale[5].

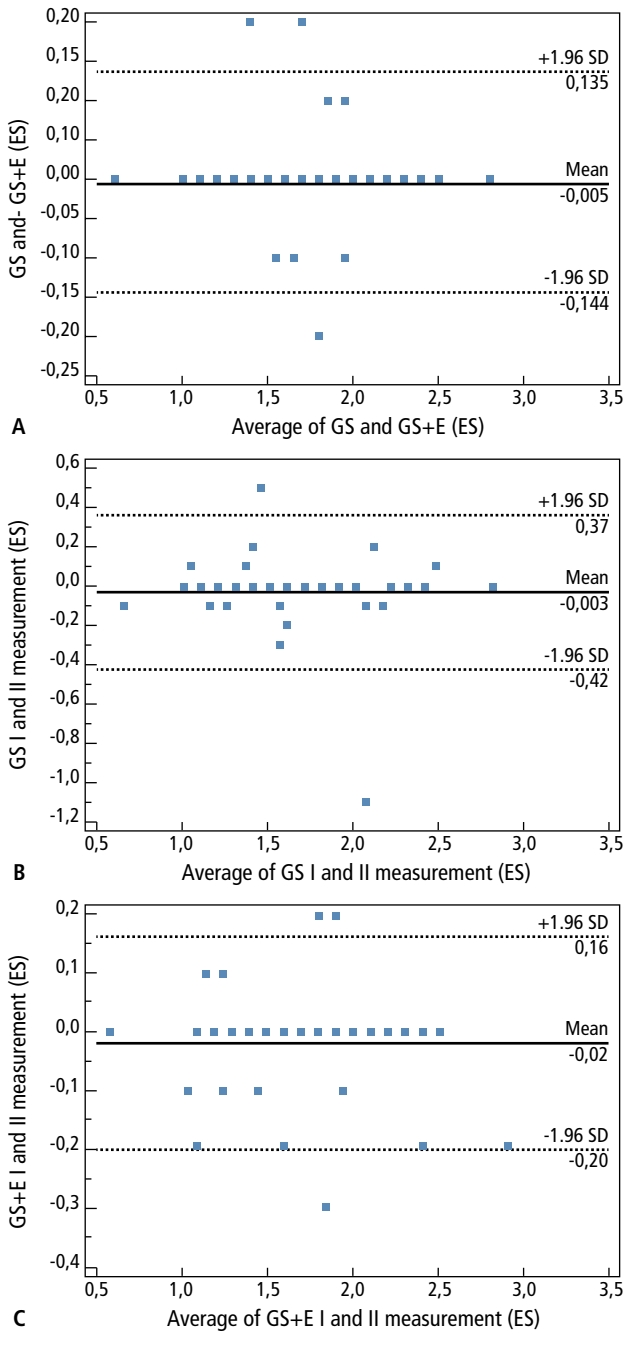
Although there is evidence in favour of a positive correlation between this semiquantitative method based on the palpation of 17 skinsites and skin punch biopsy scores, this method has several limitations such as operator dependency and low sensitivity to changes[6-8]. Studies performed with skin biopsies, US and durometry show that palpation may underestimate skin fibrosis[9,23-25]. Other methods such as ultrasound (US) and durometry, are therefore being investigated to assess SSc patients' skin[9-18].

There is evidence supporting US as an effective tool to measure SSc patients' skin thickness[9-18], but inter-observer agreement varies based on the anatomic site being evaluated with fingers rating at the lowest level[11,13,16]. Compared to hand, forearm, leg and chest, another study showed that fingers were the anatomical site featuring least intra-observer agreement in terms of ICC values[13].Widely variable inter-observer values (ranging from 1.0% to 0.0016%) were registered at proximal phalanx and forearm level[11] in a cross-sectional study where US was employed to evaluate skin thickness. This greater inter-observer variability could be linked with two factors: keeping US beam perpendicular to the skin's surface and with finger's dermis mainly lying on fibrous connective tissue rather than adipose tissue.

Fingers are useful evaluation targets since they are the earliest affected sites, but, the reliability of fingers assessment with US requires very high frequency probes and experience sonographers in order to identify dermis and subcutaneous tissue interface[11-13,15]. Two studies attained a high reproducibility when using 22 MHz and 18 MHz frequency probes to measure phalanx skin thickness[12,15].

Elastosonography is a non-invasive imaging technique that displays tissue's elasticity by providing a coloured map that is superimposed onto standard B-mode US images[18,20]. It is currently used to identify neoplasms (breast, prostate, thyroid and pancreas) to discern malignant lymph nodes from inflamed ones[26] and mostly to investigate breast conditions, since its tissue can be easily compressed by the US probe[27].

Figure 1: Bland-Altman plots displaying intra-observer (A) and inter-observer reliability (B-C) between elastrosonography and second observer using only standard B-mode or standard B-mode + elastosonography (E). 95% of the differences against the means were less than two standard deviation.



The following study offers a different and complementary approach to the one offered by other authors in a recent paper[28] and aims to investigate elastosonography's role in improving US measurement reliability regarding skin thickness measurement of SSc patients' fingers.

In this study, ICC values were 0.904 and 0.979 for intra-observer agreement with 0.726 and 0.881 for the inter-observer agreement using, respectively, only standard B-mode images and also elastosonography *(Fig. 1)*. An excellent correlation was attained between B-mode images and elastosonography measurements assessed by an expert sonographer (rho=0.99), while rho values between the two observers were 0.59 and 0.88 using, respectfully, standard B-mode and also elastosonography *(Tab. I - Scatter diagram Fig. 2)*.

Table I: Correlation between B-mode and elastosonography measurements (two readings) and the second assessment.

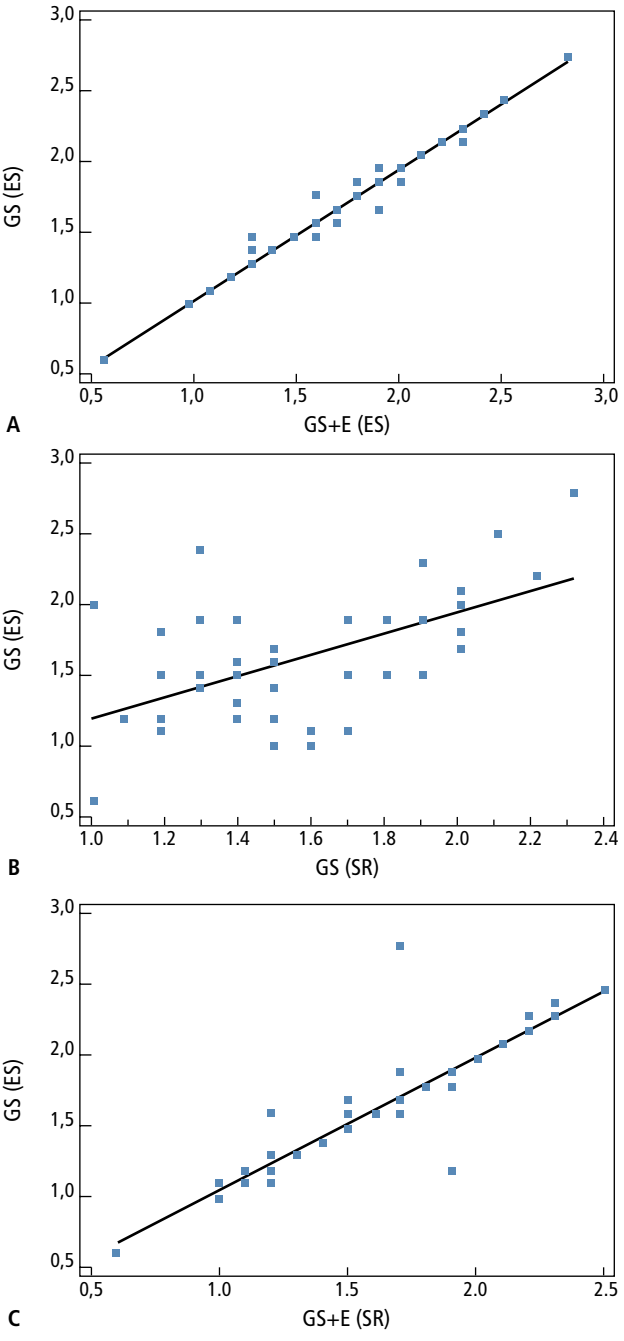
	Rho	p-value
Intra-observer (ES) B-mode vs.B-mode + elastosonography	0.99	p<0.0001
B-mode	0.90	p<0.0001
B-mode + elastosonography	0.98	p<0.0001
Inter-observer (elastosonography vs.second observer) B-mode	0.59	p<0.0001
B-mode + elastosonography	0.88	p<0.0001

Although limited by its small number of patients, intra-observer reliability having been assessed using only one set of elastosonographic images and the lack of correlation with a validated tool such as durometry[16,17], this study provides evidence regarding elastosonography's usefulness to measure finger's skin thickness by identification of dermis-hypodermis interface.

Study Case

The Rheumatology Department of the *Università Politecnica delle Marche, Jesi (Ancona), Italy* consecutively recruited twenty-two systemic sclerosis patients according to the American College of Rheumatology criteria[21]. The study was performed in compliance with the Declaration of Helsinki and approved by the local ethics committee. Patients with scars on their dominant hand's index were excluded from the study.

Figure 2: Scatter diagrams displaying correlation between B-mode and elastosonography measurements. **(A)** correlation between ES measurements using b-mode imaging only and also with elastosonography **(E)**. **(B-C)** correlation between ES and second observer's measurements using only B-mode **(B)** and also elastosonograhy **(C)**.



All patients underwent a clinical history and physical evaluation and Short-Form-36 (SF-36) along with Raynaud's Condition Score (RCS) was completed by each patient.

Method

This was a two-phase study. The objective of the first phase was to correlate US B-mode thickness measurements with elastosonography. Skin thickness was measured by an expert musculoskeletal US sonographer using only two-dimensional B-mode imaging. An elastographic coloured map was then superimposed over the B-mode grey-scale images.

The objective of the second phase was to assess elastosonography's effectiveness to improve intra- and inter-observer reliability. Elastosonography's intra-observer agreement was established by comparing the measurements attained through the first US scans with a second set performed one month later by another sonographer who was blinded about the previously attained clinical data. Both first and second measurements were attained with and without superimposed elastographic coloured map.

Inter-observer reliability of standard US images and standard US images with elastosonography mapping was assessed by comparing elastosonography's skin thickness measurements with those attained by a second observer. The second observer used the same, previously acquired elastographic images for the assessments.

Results

44 skin measurements were attained from 22 patients through standard B-mode scans and with elastosonography *(Table II)*. Each US assessment took less than 5 minutes. Standard B-mode imaging as well as standard B-mode scans combined with elastograms offered the following excellent intra-observer reliability *(Table III)*.

An excellent correlation (rho=0.99) was established between the measurements attained with elastosonography using first only B-mode imaging and later also elastosonography.

Spearman's coefficient values estimating the correlation of the measurements attained by the two observers were 0.59 using only B-mode images and 0.88 employing also elastosonography *(Table I)*.

Table II: SSc patients data

Patients demographics	
Gender (Female/Male)	20/2
Age in years, mean ±SD (range)	57.1±11.3 (36–73)
Disease duration in years, mean ±SD (range)	7.4±4.7 (1–20)
Subset: Limited/Diffuse	14/8
Phase: Oedematous/Fibrotic/Atrophic	7/11/4
mRSS, mean ±SD; median (95% CI)	11.8±9.8; 8 (4.0–19.0)
Raynaud's Condition Score	2.7±2.14; 2 (2–4)
mean ±SD; median	(95% CI)
SF-36 Patients clinical data	
Physical Functioning:	59.8±22.4; 60 (45–70)
Role-Physical:	54.6±41.5; 62.5 (25–100)
Bodily Pain:	55.0±26.4; 46.5 (41.0–71.2)
General Health:	36.5±17.8; 34.5 (28.6–44.3)
Vitality:	55.7±18.7; 55.0 (46.1–63.9)
Social Functioning:	60.5±15.0; 62.0 (50.0–72.2)
Role-Emotional:	56.0±46.4; 66.0(0–100)
Mental Health:	63.8±21.3; 70.0 (48.9–79.1)

Table III: Intra- and inter-observer reliability

	ICC (95% CI)
Intra-observer agreement	
Intra-observer B-mode	0.904 (0.830–0.946)
(ES) B-mode + elastosonography	0.979 (0.963–0.989)
Inter-observer agreement	
Inter-observer B-mode	0.726 (0.498–0.850)
(ES vs. second observer) B-mode+elastosonography	0.881 (0.792–0.933)

Statistical analysis

Statistical analysis was performed using MedCalc®, version 11.2.0.0 for Windows® XP. Intra- and inter-observer reliability was calculated using intra-class correlation coefficient (ICC). Spearman's correlation was used to calculate the correspondence between the skin thickness measurements attained using the two techniques. The correlation between US measurements skin thickness and clinical features (total mRSS, site-specific mRSS only at finger level) was assessed through Spearman's coefficient. Bland-Altman plots and scatter diagrams (with regression line used only to assist in results interpretation) with a p statistical connotation level show skin measurements agreement and correlation.

US assessment

Skin thickness measurements were taken using myLab70 XVG system (Esaote SpA - Genoa, Italy) using a broadband 6–18 MHz linear probe and an imaging software especially designed for elastosonography (ElaXto).

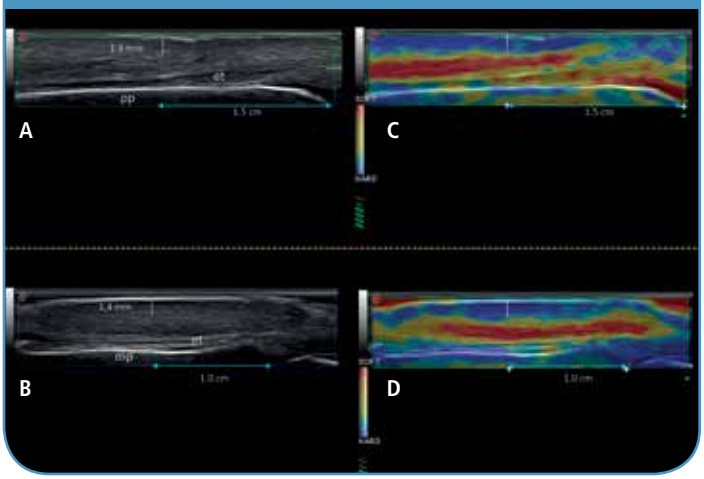
US examinations began in B-mode according to EULAR musculoskeletal US scanning guidelines[22]. The probe was placed perpendicular to the tissue with a thin layer of gel as a subtle anechoic band. The sonographer then performed an elastographic study to provide another measurement through skin's elasticity.

As described in previous studies, free-hand technique was employed with gradual, uniform, repetitive, light, manual compression and decompression to display elastographic coloured map superimposed on B-mode images[26,28]. Scan accuracy was confirmed by the system's successful feedback. All standard B-mode images and standard B-mode scans with superimposed elastograms were stored with and without electronic callipers for skin thickness measurements to be assessed in the second phase of the study.

This equipment calculates tissue elasticity according to the region of interest (ROI) average strain. ROI was therefore set to include top epidermis and bottom bony cortex taking into account that included tissue types change elastogram's coloured map. Based on strain's magnitude each pixel was assigned a different colour reflecting tissue's different elastic levels. A 5 level chromatic scale ranging from red to blue was employed, with red being softer tissue and blue harder tissue. The see-through coloured map was superimposed over B-mode images to detect the correlation between elastosonographic and standard B-mode images in real-time. Electronic callipers were placed to measure skin thickness. Epidermis-dermis and dermis-subcutis interfaces were first identified using standard US images only. Interfaces were then also identified using elastograms' color coding.

The measurements of dorsal proximal and middle phalanges of dominant hand's index finger were acquired[15]. The perpendicular US beam allowed to assess the skin overlying dorsal phalanx's middle section more easily by avoiding skin plica at joint level and possible palmar hyperkeratosis. The probe was positioned at the centre for dorsal longitudinal scan and measurements were acquired 1.5 cm and 1 cm distally at the base of proximal phalanx and middle phalanx *(Fig. 3)*.

Figure 3: Skin thickness measurements B-mode images and with elastosonography. Standard B-mode longitudinal images of dorsal proximal and middle phalanx **(AB)** and corresponding elastograms **(C-D)**, vertical white lines represent skin thickness measurements which were taken, respectively, at 1.5 cm and 1 cm distally from the bases of the proximal and middle phalanges. pp: proximal phalanx; mp: middle phalanx; et: extensor tendon.



Fingers are an ideal site to assess tissue with elastosonography, since phalanges diaphyseal bony cortex supplies an uniform plane to compress the overlying parallel positioned tissues. Fingers also have less inter-subject variability since this equipment calculates elasticity based on tissues located in the region of interest.

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