Reliability of ultrasound measurements of dermal thickness at digits in systemic sclerosis: role of elastosonography

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Abstract

Objective

To investigate the role of elastosonography to improve the reliability of the ultrasound in the measurement of the dermal thickness at finger level in systemic sclerosis (SSc).

Methods

Twenty-two patients with a diagnosis of SSc were consecutively recruited. In all patients at the second finger level of the dominant hand the dorsal aspect of proximal and middle phalanx was assessed in grey-scale and also using the elastosonography by an experienced musculoskeletal sonographer. The first step of the study was directed to explore the correlation between measurements of the dermal thickness using the grey-scale and elastosonography. Subsequently, the intra and the inter-reader reliability (between the sonographer who performed the ultrasound study and another sonographer) in the ultrasound measurements of the dermal thickness was assessed. Intra and inter-reader reliability was calculated using intra-class correlation coefficient (ICC) and illustrated by Bland-Altman plots.

Results

The ICC values were 0.904 and 0.979 for the intra-observer agreement, and 0.726 and 0.881 for the inter-observer agreement, using only the grey-scale and also the elastosonography, respectively. An excellent correlation was obtained between measurements in grey-scale and adopting the elastosonography by the experienced sonographer (rho=0.99), while the rho values between the two readers were 0.59 and 0.88, using the conventional technique and also the elastosonography, respectively.

Conclusion

Elastosonography can improve the reliability of the US measurements of the dermal thickness at finger level in patients with SSc, helping for the identification of the interface dermis/hypodermis.

Key words

systemic sclerosis, skin, dermal thickness, ultrasound, elastosonography

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Introduction

Skin involvement in systemic sclerosis (SSc) is not only a disabling feature but also a predictor of visceral involvement and increased mortality (1-4). The modified Rodnan skin score (mRSS) is the standard outcome measure of skin involvement in SSc. Evidence in favour of a positive correlation between this semiquantitative method based on the palpation of 17 skin sites and skin punch biopsy scores was found (5). However, mRSS has several limitations, including operator dependence and low sensitivity to change over time (6-8). Thus, other alternative methods, such as ultrasound (US) and durometry (using digital hand-held, spring-loaded devices), have been investigated in the assessment of skin in patients with SSc (9-18). Even if both US and durometry have showed to be reliable methods, the inter-observer agreement depends on the anatomic site, being lower at finger than at other levels (11, 13, 16).

Elastosonography is an imaging technique that allows a non-invasive visualisation of the elastic properties of tissues under examination providing a coloured map superimposed to the grey scale US imaging (18, 20).

The main aim of the present study was to investigate the role of elastosonography to improve the reliability of US in the measurement of the dermal thickness at finger level.

Materials and methods

Patients

Twenty-two patients affected by SSc, fulfilling the American College of Rheumatology criteria, were consecutively recruited at the Rheumatology Department of the Università Politecnica delle Marche (Ancona, Italy) (21). Exclusion criteria included: amputations and scars on the second finger of the dominant hand. History and complete physical evaluation were obtained by an experienced rheumatologist and all patients completed the Short-Form-36 (SF-36) and the Raynaud's Condition Score (RCS).

Study design

The study was composed of two main steps. The first step was aimed at exploring the correlation between the measurements of the dermal layer thickness using the grey-scale and the elastosonography. An experienced sonographer (ES) in musculoskeletal US, measured the dermal thickness using only the conventional two-dimensional B-mode and, successively, with the help of the elastographic coloured map superimposed on the grey-scale images.

In the second step, the additional value of the elastosonography in improving the intra- and inter-reader reliability was investigated.

Intra-reader agreement of the ES was calculated by comparing the dermal thickness measurements obtained during the US scanning (first measurement) and, one month after, under blinded conditions, using the images stored at baseline US examination (second measurement). Both first and second measurements were taken with and without the superimposed elastographic coloured map.

Inter-reader reliability of grey-scale US and grey-scale plus elastosonography was estimated comparing the dermal thickness measurements taken by the ES with those obtained by a second reader (SR) who works and has been trained in the same department. SR used the same images acquired by the ES for her assessments.

The study was carried out according to the Declaration of Helsinki and it was approved by the local ethics committee. Informed consent was obtained from all the patients.

US examination

Dermal thickness measurements were obtained using a myLab70 XVG (Esaote SpA - Genoa, Italy) equipped with a broadband 6–18 MHz linear probe and a dedicated software (ElaXto) allowing elastosonography imaging.

The US examinations started in B-mode following the scanning indications provided in the EULAR guidelines of musculoskeletal US (22).

The probe was placed perpendicular to the skin with a thin layer of gel detectable as a subtle anechoic band superficial to the hyperechoic line of the epidermis.

The measurement of the dermal thickness was calculated after setting the US

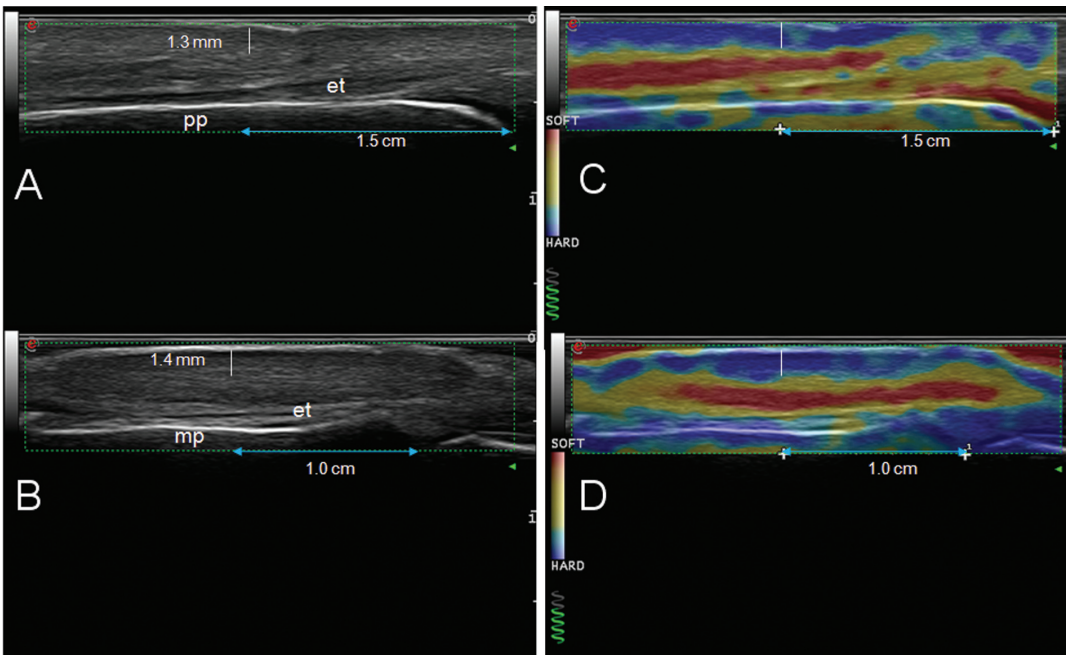

Fig. 1. Dermal thickness measurements in grey-scale and with elastosonography. Longitudinal dorsal views of the proximal and middle phalanx in grey-scale (**A-B**) and the corresponding elastograms (**C-D**), being the vertical white lines representative of the measurements of the dermal thickness, taken at 1.5 cm and 1 cm distally from the bases of the proximal and middle phalanx, respectively. pp: proximal phalanx; mp: middle phalanx; et: extensor tendon.

system in order to optimise the visualisation in B-mode of the interface between the dermis and the subcutaneous tissue. Then, the sonographer carried out the elastographic examination to provide another measurement using the elasticity images. The values of both these measurements were obtained by the ES and considered the "gold standard". All US images only in grey-scale and with the superimposed elastograms were also stored with and without electronic callipers to allow the measurements of the dermal thickness in the second part of the study.

In order to visualise the elastographic coloured map superimposed on the B-mode imaging, the free-hand technique was adopted applying gradual, uniform, repetitive, light, manual compression and decompression, as described in previous studies (26, 28).

The system provided a positive feedback to the sonographer indicating that the scanning was properly performed. Of note, the system calculates the elasticity according to the average strain inside the region of interest (ROI). Thus, since the types of tissues included in the box fundamentally change the elastogram coloured map, the ROI was set to include the epidermis on the top and the bony cortex at the bottom. Depending on the magnitude of strain (related to the elastic properties of the tissues) one colour was assigned to each pixel with a scale which included 5 main levels ranging from red (tissues with greatest strain, *i.e.* softest tissue) to blue (hardest tissue).

The translucent coloured map, superimposed on the B-mode imaging allows to recognise in real-time the relationship between elastosonography and grey-scale images.

Electronic callipers were placed to measure the dermal thickness firstly by identifying both the epidermis/dermis and dermis/subcutis interfaces on the grey-scale images, and secondly also by using the different colours on the elastograms.

The measurements were obtained at two sites of the dominant hand: the dorsal aspect of proximal and middle phalanx of the second finger (15). The skin overlying the middle part of the phalanx on the dorsal aspect is the ideal region of the finger to be assessed being more easily to obtain a perpendicular US beam, avoiding the skin plica at joint level, and the possible hyperkeratosis of the palmar aspect.

In longitudinal dorsal scan the probe was placed in the centre (visualising the course of the extensor tendon), and the measurements were taken 1.5 cm and 1 cm distally to the base of the proximal phalanx and the middle phalanx, respectively (Fig. 1).

In skin assessment, the finger is the ideal site for elastosonography, because the bony cortex of the phalanxes diaphysis provides an uniform plane to compress the overlying tissues which are arranged in parallel levels. Furthermore, since the system calculates the elasticity according to the tissues included in the ROI, the finger represents an anatomic site with less inter-subject variability.

Statistical analysis

Statistical analysis was performed using MedCalc®, version 11.2.0.0 for Windows XP.

The intra- and inter-observer reliability was calculated using the intra-class correlation coefficient (ICC).

Spearman's correlation was used to calculate the correlation between the measurements of the dermal thickness, obtained adopting the two techniques by the ES and provided by the ES and the SR.

A graphic representation illustrating the agreement and the correlation between the dermal measurements was also provided using Bland-Altman plots and scatter diagrams (with the regression line only in order to help the interpretation of the results), with a level of statistical significance of $p<0.05$ (two-sided) (23).

The correlation between the US measurements of the dermal thickness and

Table I. Demographic and clinical data of SSc patients.

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, mean±SD; median (95% CI)		2.7±2.14; 2 (2–4)
SF-36	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 II. Intra- and inter-observer reliability between the ES (two readings) and the SR using only grey-scale (GS) or grey-scale plus elastosonography.

		ICC (95% CI)
Intra-observer (ES)	GS	0.904 (0.830–0.946)
	GS *plus* Elastosonography	0.979 (0.963–0.989)
Inter-observer (ES *vs*. SR)	GS	0.726 (0.498–0.850)
	GS *plus* Elastosonography	0.881 (0.792–0.933)

Table III. Correlation between measurements obtained using grey scale (GS) and elastosonography by the ES (two readings) and the SR.

		Rho	*p*-value
Intra-observer (ES)	GS *vs*. GS *plus* Elastosonography	0.99	$p<0.0001$
	GS	0.90	$p<0.0001$
	GS *plus* Elastosonography	0.98	$p<0.0001$
Inter-observer (ES *vs*. SR)	GS	0.59	$p<0.0001$
	GS *plus* Elastosonography	0.88	$p<0.0001$

the clinical features (total mRSS, site-specific mRSS only at finger level) was assessed by Spearman's coefficient.

Results

Demographic and clinical data of SSc patients are reported in Table I.

Forty-four dermal measurements were obtained using both grey-scale imaging and elastosonography in 22 patients. US examination took not more than 5 minutes per patient.

Intra- and inter-observer reliability ICC values for the dermal measurements are shown in Table II.

An excellent intra-observer reliability was always reached by the ES, adopting both conventional B-mode technique (ICC=0.904) and the grey-scale images plus elastograms (ICC=0.979). ICC value for inter-observer reliability was 0.726 using the grey-scale while when the same observer (SR) had access also to elastographic images the ICC value was 0.881 (Table II).

Agreement rates of the intra- and inter-observer reliability were also showed by Bland-Altman plots (Fig. 2). The most of 95% of the differences against the means were less than two standard deviation.

An excellent correlation (rho=0.99) was found between the measurements obtained by the ES using first only grey scale imaging and successively also elastosonography. Spearman's coefficient values estimating the correlation of the measurements obtained by the two observers were 0.59 using only the grey scale and 0.88 adopting also elastosonography (Table III). Scatter diagrams are illustrated in Figure 3.

No correlation was found between the measurements of digital dermal thickness (using the help of the elastosonography) and the mRSS (rho=-0.22; p=0.10) or the skin score at finger level (rho=-0.03; p=0.78).

Discussion

To the best of our knowledge, this is the first study providing evidence in favour of the peculiar application of the elastosonography to improve the reliability in the sonographic measurements of the digital dermal thickness in patients with SSc.

Skin involvement is the clinical hallmark of SSc and it is currently measured semiquantitatively using the mRSS which is yet considered the "gold standard", even if studies conducted with skin biopsies, US and durometry indicated that palpation may underestimate the skin fibrosis (9, 23-25).

Of note, despite the few investigations available in the literature, there is evidence supporting US as a valid tool for measuring dermal thickness in SSc (9-15).

The finger is an interesting target to examine because it represents the earliest affected site. However, especially at this level, the identification of the interface between dermis and subcutaneous tissue requires not only very high frequency probes, but also experience and expertise of the sonographer, as demonstrated by conflicting results in terms of reliability in the US assessment of the finger (11-13, 15).

In a cross-sectional study, focused on the US measure of the dermal thickness, a wide variability of the inter-observer values (ranging from 1.0% to 0.0016%) was reported at proximal phalanx and forearm level, respectively (11). In another study, the finger resulted the anatomic site with the lowest inter-observer agreement in terms of ICC values compared to hand, forearm, leg and chest (13). Possible explanations of the higher variability in measuring dermal thickness at finger level include the difficulty to obtain and maintain the US beam direction perpendicular to the skin surface, especially with slender

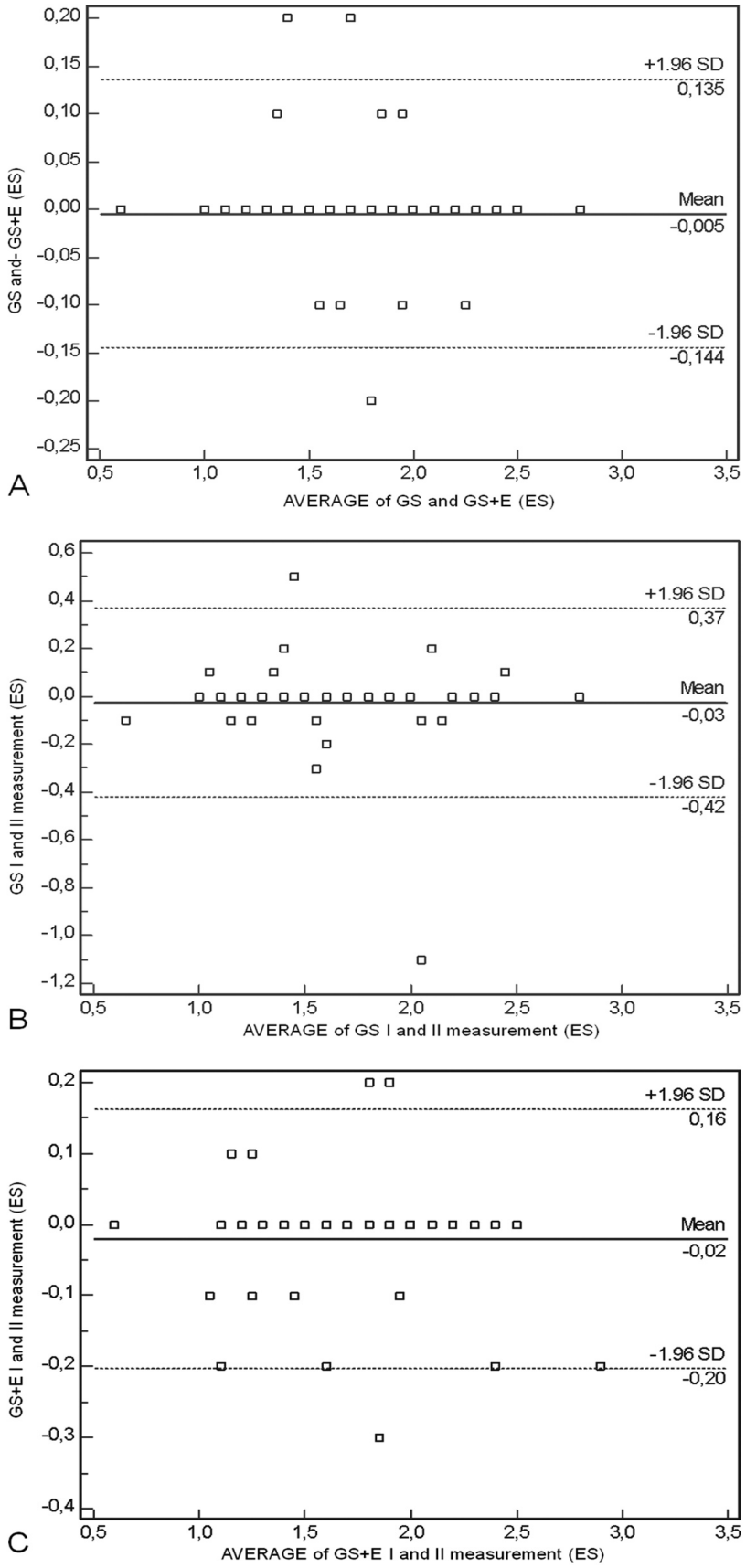

Fig. 2. Intra- and inter-observer agreement. Bland-Altman plots illustrating intra-observer (A) and inter-observer reliability (B-C) between the ES and the SR using only grey-scale (GS) or GS plus elastosonography (E).

fingers, and the fact that the dermis lies mainly on fibrous connective instead of adipose tissue. High reproducibility was obtained in the US dermal measurements at the phalanx level in two studies, using 22 MHz and 18 MHz frequency probes (12, 15).

Intra-observer values obtained in the present study by the ES using only the grey-scale images are in agreement with those reported in the literature (12-15).

Nowadays, the application of elastosonography in the clinical practice is mainly in the differential diagnosis of neoplasms (breast, prostate, thyroid and pancreas), as well as for distinguishing between malignant or inflammatory lymph nodes (26). The first and frequently investigated target is the breast, because it is readily accessible to compression with the US probe (27).

The present study represents a different, complementary approach for skin elastographic assessment in SSc patients, with respect to that proposed by Iagnocco *et al*. in a recent paper (28). They showed different elastographic patterns in healthy controls and SSc patients in assessing the skin at elbow level, while this result was not found at finger dorsal aspect.

In the present study, the role of the elastosonography in increasing the reliability in the US measurements of the dermal thickness at finger level was investigated. We found higher levels of agreement and correlation between the measurements of the dermal thickness by the ES and SR helped by elastosonography, with respect to the values obtained by the same investigators adopting only the conventional technique.

No correlation between the measurements of the dermal thickness at finger level and the mRSS was found, either in terms of total score or values of skin score site-specific (limited to the fingers). In the literature, the correlation of US measurements of dermal thickness to mRSS is controversial because the value of the mRSS is probably related not only to the skin thickness, but also to skin hardness, texture and fixation (16, 29).

We could not find any correlation between sonographic measurements of

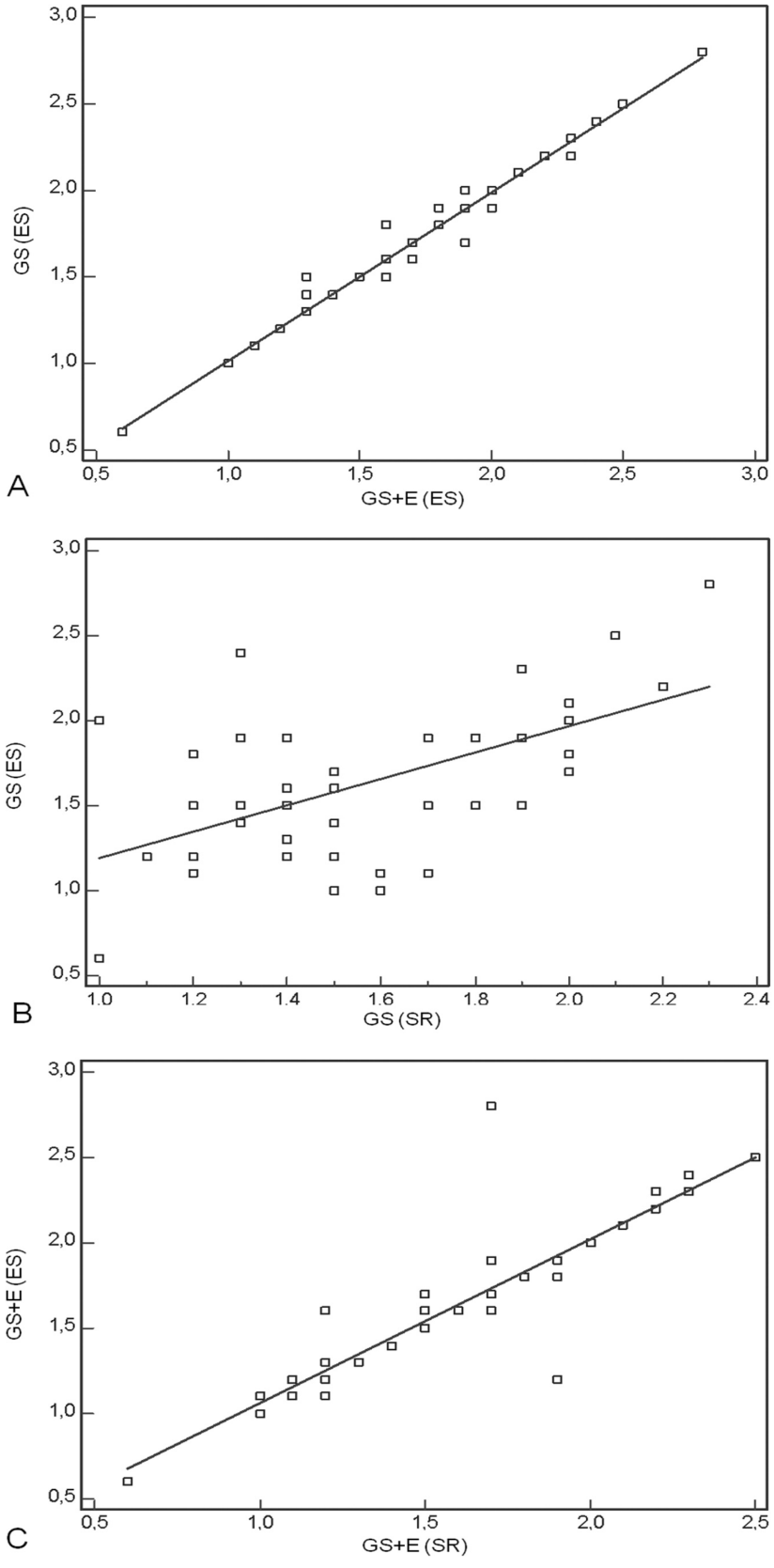

Fig. 3. Correlation between measurements in grey-scale and with elastosonography. In **A**, scatter diagrams showing the correlation between the measurements obtained by the ES both using only grey-scale imaging (GS) and also elastosonography (E). In **B-C**, scatter diagrams showing the correlation between the measurements obtained by the ES and the SR using only GS (**B**) and also E (**C**).

the dermal thickness and the RCS (rho=-0.03).

This study presents some limitations. First, the small number of patients investigated. Second, the intra-observer reliability assessment was based on evaluations performed using a single set of images acquired by the ES. Finally, no correlation was made with durometry which represents a validated tool for evaluation of skin involvement (16, 17).

In conclusion, the present study provides evidence in favour of the usefulness of elastosonography in patients with SSc improving the reliability in the US dermal measurements at finger level facilitating the identification of the dermis/hypodermis interface.

These results justify the use of elastosonography to measure the dermal thickness at finger level in larger cohorts of patients with SSc for further testing its validity which represents the essential requirement for developing investigations aiming at monitoring dermal thickness in SSc also in multicentre studies.

However, these preliminary results have to be confirmed in a larger cohort of patients.

Key messages

- The assessment of the skin disease in SSc remains a challenge for rheumatologists.
- Elastosonography, a relatively new US technique, can improve the reliability in the dermal thickness measurements in SSc.

Authors' contributions

LDG made substantial contributions to conception and study design, participated in the acquisition, analysis and interpretation of data, performed the ultrasound assessments, and prepared the draft of the manuscript.

EF participated in the study conception and design, analysis and interpretation of data, in drafting the manuscript, revising it critically for important intellectual content.

RG made substantial contributions in the analysis and interpretation of the ultrasound images allowing the determination of the inter-observer reliability.

MT made substantial contributions in the acquisition of data and was involved in patient recruitment.

MG made substantial contributions in the analysis and interpretation of data and in drafting the manuscript and was involved in patient recruitment.

RDA made substantial contributions in the acquisition of data and in drafting of the manuscript.

FS participated in the study development and recruitment of patients, conducted data assessment and statistical analysis, and gave final approval of the version to be published.

WG provided substantial input to the study design, analysis and interpretation of data, and gave final approval of the version to be published. All authors approved the final version of the manuscript.

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