Ultrasound for day-to-day clinical use: construction of a simple discriminator between healthy skin and thickened systemic sclerosis skin

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Abstract

Objective

Distinction of dermal thickening at fingers is paramount in recognition of systemic sclerosis (SSc). Evaluation of skin thickening by modified Rodnan skin score (mRSS) might be challenging. Simple and practical tools are needed to help distinguishing (non-) thickened skin in daily practice. High frequency ultrasonography (HFUS) can reliably measure dermal thickness (DT). In this pilot study we search for a DT cut-off value (as a simple HFUS discriminator) to distinguish between healthy control (HC) and SSc skin at the left index finger (F2L).

Methods

DT evaluated by HFUS (18MHz probe) in SSc patients (2013 ACR/EULAR criteria) was compared with HC in a cross-sectional study. A cut-off value was selected by receiver operating characteristic (ROC) curve analysis.

Results

63 consecutive SSc patients (mean age 52±14 SD, 78% female) and 48 HC (mean age 36±14 SD, 62% female) underwent HFUS. Mean DT at F2L was 1.44 mm (± 0.39 SD) in SSc patients and 1.06 mm (± 0.19 SD) in HC. Based on ROC-curve analysis, a DT cut-off of 1.5 mm is proposed as simple HFUS discriminator between HC and SSc, at a specificity of 1 and a sensitivity of 0.32. The final model had an area under the curve of 0.83 (95%CI 0.75–0.90).

Conclusion

A simple HFUS discriminator between skin thickness of HC versus SSc, i.e. DT as measured at F2L, at a cut-off of 1.5 mm, is proposed for daily use in rheumatology clinics. Further validation should be executed through prospective multicentric cohorts.

Key words

skin, dermal thickness, systemic sclerosis, ultrasound

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Introduction

Systemic sclerosis (SSc) is a complex connective tissue disease characterised by autoimmunity, vasculopathy and fibrosis of the skin and internal organs (1). Detection of skin thickening in the fingers, a hallmark clinical feature of the disease, is key in recognising SSc. Currently, skin thickening is evaluated by clinical palpation using the semi-quantitative modified Rodnan skin score (mRSS) (2). This established outcome measure has, however, substantial inter-rater variability and is highly dependent on the training and experience of the rater (3, 4). Simple and practical tools are needed to help distinguishing (non-) thickened skin in daily practice.

High frequency ultrasonography (HFUS) has proven to reliably measure dermal thickness (DT) in skin, with a good-to-excellent inter-/intra-rater reliability in both SSc patients and healthy controls (HC) (5-8). HFUS is an easy applicable and non-invasive tool, without radiation exposure and well tolerated by patients. Moreover, HFUS with linear transducers of at least 18 MHz, recommended for skin evaluation (9), are nowadays widely available in rheumatology clinics as standard musculoskeletal probes on ultrasound machines. Evaluation for increased DT by HFUS at just one position, the finger (*i.e.* where skin thickening starts in SSc), can further increase feasibility in daily practice.

Therefore, in this pilot study, we searched for a HFUS measured DT cut-off value in mm (= the simple HFUS discriminator) at the left index finger (F2L) to distinguish between healthy and systemic sclerosis skin.

Methods

Ethics

The study was approved by the local Ethics Committee of Ghent University Hospital (EC/2008/385 and EC/2019/1633) and conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each participant before study enrolment.

Study design

This is a *post-hoc* analysis of a cross-sectional study, of which the acquisition of the dataset was previously published (5).

Study population

This is a *post-hoc* analysis of a reliability study concerning HFUS in an unselected cohort of SSc patients visiting the Ghent University Hospital for their annual SSc-related follow-up appointment (5). Patients were classified as SSc according to the 2013 American College of Rheumatology (ACR)/EULAR classification criteria for SSc, and stratified according to LeRoy and Medsger into limited SSc, limited cutaneous SSc (LcSSc) and diffuse cutaneous SSc (DcSSc), based on the degree of their skin involvement (10, 11). Skin thickening was assessed by the mRSS score, using clinical palpation of 17 standard skin regions, scoring involvement on a 0–3 categorical scale (maximum of 51) (4). For this analysis, only patients with skin involvement, defined as a mRSS score above 0, therefore classified as LcSSc or DcSSc, were included. Disease duration was calculated from first non-Raynaud symptom. Non-matched HC had been recruited from the environment of Ghent University Hospital (*i.e.* staff of Ghent University Hospital, university students and family of recruited patients). Data on demographics and anthropometric measurements of the subjects were recorded.

HFUS examination

HFUS examination was performed using a Logiq S8 ultrasound system (GE Healthcare, Chalfont St Giles, UK), equipped with an 18 MHz linear probe, in B- mode. During the examination, each subject was placed in supine position with a pillow under the head. Images were obtained by placing the probe directly over the skin, using a moderate layer of water-based ultrasound gel as a coupling agent between the skin surface and the probe. While the probe was held perpendicular to the skin surface, probe pressure was avoided to ensure that skin thickness did not change due to compression. Images were obtained at the midway dorsum of the proximal phalanx of the left index finger (F2L). The obtained images show the cutaneous layers: epidermis, dermis and hy-

podermis/subcutis. DT (expressed in millimetres [mm]) was measured as the distance between the epidermis-dermis interface and the dermis-subcutis interface using an electronic calliper. DT per image was determined by adding the obtained values for three measurements and dividing their sum by three. In each subject, the HFUS examination was performed twice by the same rater (experienced in musculoskeletal ultrasound for >9 years), resulting in 2 images per subject, dermal thickness (DT) was calculated as the average DT of the 2 images.

Statistical analysis

For descriptive purposes, absolute numbers with percentages are presented for categorical variables and means with standard deviation (SD) for continuous variables. Receiver operating curve (ROC) analysis was performed with the variable DT at F2L in HC *versus* SSc patients. A cut-off value, as simple HFUS discriminator, for DT at F2L in HC *versus* SSc patients, was selected by use of ROC-curve analysis, based on a trade-off between sensitivity and specificity. Positive and negative predictive values (PPV and NPV) were calculated using the obtained sensitivity and specificity values, and an assumed prevalence of SSc of 1/10.000 in the population (12, 13). Correlations of variables were assessed with the Spearman's rank correlation test. Statistical analyses were performed using R Statistical Software version 4.3.1 (14) and the tidymodels package (15).

Results

63 consecutive SSc patients and 48 HC underwent HFUS (schematic representation of HFUS measurement in Supplemental Figure S1). Demographics and clinical characteristics of SSc patients and HC are outlined in Table I. In both groups, the majority of subjects were female. 84% of SSc patients had limited cutaneous involvement, 16% diffuse. The mean mRSS of the left index finger in SSc patients was 1.5 (on a total score of 3). All subjects were Caucasian, with the exception of 1 Asian LcSSc patient.

DT of the left index fingers of all subjects are depicted in Figure 1A. Mean DT was 1.44 mm (± 0.39 SD) in SSc patients and 1.06 mm (± 0.19 SD) in HC. Using ROC-curve analysis, DT of the left index finger had an area under the curve of 0.83 (95%CI 0.75 to 0.90) (Fig. 1B).

Age and sex showed no strong correlations with DT (age HC: r= -0.20, p=0.18; age SSc patients: r=0.05, p=0.68; sex HC: r= -0.42, p=<0.01; sex SSc patients: r= -0.23, p=0.07).

A DT cut-off of 1.5 mm, with a specificity of 1 (95%CI 0.93 to 1) and a sensitivity of 0.32 (95%CI 0.22 to 0.44), is proposed as simple HFUS discriminator between HC and SSc skin at the left index finger (red dashed cut-off line in Figure 1A). A DT cut-off of 1.25 mm rendered a specificity of 0.79 (95%CI 0.66 to 0.88) and a sensitivity of 0.70 (95%CI 0.58 to 0.80) (blue dashed cut-off line in Figure 1A). When used in a population with a SSc prevalence of 1/10.000 (12, 13), the cut-off of 1.5 mm has a calculated PPV of 1 (95% CI 0.9665 to 1.0000) and NPV of 0.99993 (95%CI 0.9664 to 1.0000), while the cut-off of 1.25 mm has a PPV of 0.00335 (95%CI 0.0003 to 0.0397) and a NPV of 0.99996 (95% CI 0.9665 to 1.0000).

Table I. Demographics and clinical characteristics.

	SSc patients (n=63)	Healthy controls (n=48)
Age (years), mean ± SD	52 ± 14	36 ± 14
Sex (male/female), n(%)	14(22)/49(78)	18(38)/30(62)
Total mRSS (/51), mean ± SD	7.3 ± 7.2	0.0 ± 0.1
mRSS F2L (/3), mean ± SD	1.5 ± 0.7	0.0 ± 0.1
LcSSc/DcSSc, n(%)	53(84)/10(16)	
Disease duration (years), mean ± SD	7.7 ± 7.3	

SSc: systemic sclerosis; n: number; SD: standard deviation; mRSS: modified Rodnan skin score; F2L: Finger 2 left; LcSSc: limited cutaneous systemic sclerosis; DcSSc: diffuse cutaneous systemic sclerosis.

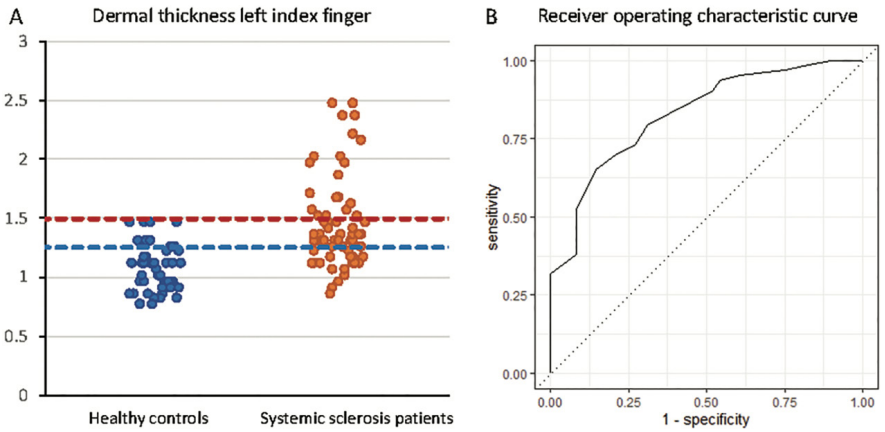

Fig. 1. Dermal thickness of the left index finger in healthy controls and systemic sclerosis patients.
A: Dermal thickness of the left index finger (in millimetre), measured by high frequency ultrasound, in healthy controls (HC) and systemic sclerosis (SSc) patients. Proposed cut-offs for dermal thickness of 1.5 mm (red dashed line) and 1.25 mm (blue dashed line) are depicted.
B: Receiver operating characteristic (ROC) curve analysis for dermal thickness at the left index finger in HC and SSc patients, with an area under the curve of 0.83 (95% confidence interval 0.75 to 0.90).

Discussion

A simple HFUS discriminator between skin thickness of HC versus SSc patients, *i.e.* dermal thickness as measured at the left index finger, at a cut-off of 1.5 mm, is proposed for daily use in rheumatology clinics, to facilitate the detection of thickened skin.

Up until now, the only available tool in clinical practice for detection of thickened skin, *i.e.* skin palpation and mRSS, is known to be highly dependent on the training and experience of the rater (3, 4). HFUS has shown to reliably measure DT in skin, even after minimal training (5-8). Measuring

DT of just 1 position (the finger, where skin thickening starts in SSc) further increases the feasibility in daily clinical practice.

Our DT cut-off of 1.5 mm has a specificity of 1, ruling out false positives, as no healthy controls in this cohort had a DT of more than 1.5 mm at the left index finger. This value corroborates with the recent findings of DT in fingers of HC in other European cohorts (7, 16). In Moore *et al*. (6), the mean DT at the left middle finger in HC was relatively thick (1.48 mm), however with a higher standard deviation (0.276), possibly reflecting less precision in DT measurement by the ultrasound equipment 20 years ago.

Li *et al*. found a cut-off for skin thickness at the right index finger of 1.3 mm, with 87.1% sensitivity and 96.8% specificity (17). However, they measured total skin thickness (epidermis and dermis) and not DT (which is proposed by Moore *et al*. (6), to overcome the poor reliability of epidermis measurements), and investigated a Chinese population while our population was predominantly Caucasian.

Corresponding to a relatively low sensitivity of 0.32, the DT cut-off of 1.5mm should be regarded as a confirmation of thickened skin, not as an exclusion of skin thickening below the cut-off. It can be a simple way to alert clinicians that they are dealing with definite skin thickening and an additional tool in creating awareness of the fibrotic hallmark of SSc in non-SSc experts.

Combining DT by HFUS with other techniques could further improve distinction between SSc and healthy skin. A recent study showed that adding skin stiffness, as measured by shear wave velocity, to HFUS-measured total skin thickness, improved the ROC-curve for the sum of 6 skin sites (AUC of 0.923 compared to 0.789 for HFUS alone) (18). However, probes for these measurements are nowadays not yet widely available and this evaluation may be more time-consuming as 6 sites need to be assessed.

The strength of our study lies in the creation of a simple tool which could help the clinical rheumatologists in every day practice, in the detection of thickened skin and diagnosis of SSc patients. Of note, our study is in accordance with the recent recommendations about the execution and reporting of skin ultrasound in SSc (9).

Some limitations have to be considered. First of all, this is a single centre study with a relatively small sample size and a homogenous population (Caucasians) in terms of ethnicity. Also, and importantly, HC were not age- and sex-matched. In our cohort, no strong correlations of DT with age and sex were observed. Only sex in HC showed a significant but only moderate correlation with DT (r= -0.42). Likewise, concerning the finger, also Santiago *et al*. (7) only found a moderate correlation of dermal thickness with sex (beta coefficient value of -0.403), but not with age. This corroborates with our findings at the finger in HC. The possibility of age-, sex- and even BMI- or ethnicity-specific DT cut-offs should be further investigated, potentially increasing test sensitivity without impairing specificity.

Further validation is necessary and should be executed through prospective and multicentric cohorts using standardised methodology as described in recent recommendations (9), further investigating the impact of different ethnic backgrounds, skin types, age, sex and BMI.

Conclusion

A simple HFUS discriminator between skin thickness of HC *versus* SSc is proposed, *i.e*. DT as measured at the left index finger, at a cut-off of 1.5 mm. Further validation should be made through prospective multicentric cohorts.

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