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JOÃO CARLOS REBELO LIMA

Ultrasound assessment of dermal thickness and skin stiffness in undifferentiated connective tissue disease at risk for systemic sclerosis

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PROFESSOR DOUTOR JOSÉ ANTÓNIO PEREIRA DA SILVA

DOUTORA TÂNIA LOUZA SANTIAGO

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Ultrasound assessment of dermal thickness and skin stiffness in undifferentiated connective tissue disease at risk for systemic sclerosis.

João Carlos Rebelo Lima[1]

Tânia Louza Santiago[1,2]

José António Pereira da Silva[1,2*]

1- Faculty of Medicine, University of Coimbra, Portugal

2- Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

***Endereço Institucional**

José António Pereira da Silva

Centro Hospitalar e Universitário de Coimbra – Reumatologia

Praceta Prof. Mota Pinto C. Postal: 3030-075 Localidade: COIMBRA

Correio eletrónico: jdasilva@ci.uc.pt

ABBREVIATIONS

ANAs – Antinuclear antibodies

DT - Dermal thickness

EULAR - European League Against Rheumatism

HFUS - High-frequency ultrasound

mRSS - Modified Rodnan Skin Score

NVC - Nailfold videocapillaroscopy

RP - Raynaud´s Phenomenon

SSc - Systemic Sclerosis

SWE - Shear-wave elastography

SWV - Shear-wave velocity

UCTD-risk-SSc - Undifferentiated Connective Tissue Disease at risk for SSc

VTIQ - Virtual Touch Imaging and Quantification

ABSTRACT

Background: High-frequency ultrasound (HFUS) and shear-wave elastography (SWE) allow an objective assessment of skin involvement in systemic sclerosis (SSc) patients. Till now it has been applied to patients with established diagnosis. However, there is no data concerning its application in Undifferentiated Connective Tissue Disease at risk for SSc (UCTD-risk-SSc), i.e., patients with Raynaud's phenomenon (RP) and either SSc marker autoantibodies or typical capillaroscopic findings or both, not satisfying classification criteria for SSc. Our aim was to compare ultrasound-dermal thickness (DT) and skin stiffness using HFUS and SWE, in UCTD-risk-SSc and healthy controls.

Methods: Forty UCTD-risk-SSc patients and 40 age- and gender-matched healthy controls were included. Ultrasound-DT was measured using an 18MHz probe, and skin stiffness [i.e. shear-wave velocity (SWV) values] using the Virtual Touch Imaging and Quantification (VTIQ) software with a 9MHz probe, at the 17 Rodnan skin sites. The Modified Rodnan Skin Score (mRSS) was, by definition, zero in all sites, both in cases and controls. Continuous data were expressed as the mean (SD), and Mann-Whitney U test and t-student test was performed to compare differences between the groups, where variables were not normally distributed or normally distributed, respectively. Associations between variables were analyzed using the Spearman's correlation.

Results: SWV values were significantly higher in patients with UCTD-risk-SSc compared with controls at the hands and fingers, bilaterally. Higher values of ultrasound-DT were found in the left thigh, left leg, right and left foot, face, and hands bilaterally, although differences were only significant at the hands, compared with controls. There was no significant correlation between ultrasound-DT and stiffness at the same skin site.

Conclusions: This study provides the first evidence suggesting that ultrasound-DT and skin stiffness can discriminate patients with UCTD-risk-SSc from healthy controls. Prospective studies including a larger number of patients with different subsets of UCTD-risk-SSc are needed to investigate diagnostic and prognostic value of the ultrasound parameters in this group.

KEY WORDS

Dermal thickness, Skin stiffness, High-frequency ultrasound, Elastography, Scleroderma.

INTRODUCTION

Systemic Sclerosis (SSc) has a huge impact on quality of life with a substantial emotional and economic burden.[1,2] Skin involvement is an important marker of SSc activity, severity and prognosis making its assessment a key issue in clinical practice and research.[3,4,5] In addition, the extent of skin involvement and its rate of progression is associated with survival, internal organ involvement and functional disability.[1] The Modified Rodnan skin score (mRSS), the current gold standard to evaluate skin involvement, is a semi-quantitative score based on skin palpation of 17 skin sites, and is often used as primary or secondary outcome in clinical trials.[5,6,7] Early detection of skin involvement represents therefore a unique opportunity to try and avoid or delay irreversible skin and organ damage.[1]

Undifferentiated Connective Tissue Disease at risk for SSc (UCTD-risk-SSc), previously known as very early/early SSc, is a condition that has raised a lot of interest over the last decade, with Raynaud´s Phenomenon (RP) being the hallmark clinical manifestation.[8] UCTD-risk-SSc is characterized by RP associated with nailfold videocapillaroscopy (NVC) findings typical of SSc and/or SSc marker autoantibodies[8] in patients that do not satisfy the 2013 European League Against Rheumatism (EULAR) criteria for definite SSc.[9] This condition can be divided in three subsets: Subset 1, characterized by RP associated with capillaroscopic scleroderma pattern and positive SSc autoantibodies; subset 2 with RP associated with positive SSc antibodies and no capillaroscopic scleroderma pattern; and, subset 3 with RP associated only with capillaroscopic scleroderma pattern and negative autoantibodies.[8] Predicting which UCTD-risk-SSc patients evolve to definite SSc has always been a difficult, albeit valuable, task mainly due to the absence of true predictive biomarkers.[1] Nowadays, the only acceptable clinical strategy consists in following these patients, closely, looking for early organ involvement.[1,10] A prospective study, with a 20 years period of follow up, showed that approximately 50% of patients with UCTD-risk-SSc evolve to definite SSc.[8,11] This differs for each subset: 79,5% in subset 1, 35,4% in subset 2 and 25,8% in subset 3.[8,11] Identifying these patients within the therapeutic window of opportunity represents an important unmet medical need in SSc.[2]

Over the last three decades, increasing evidence supports the application of skin ultrasound as a diagnostic and monitoring tool in clinical practice and research.[5] This has been made possible through technological improvements, including higher frequency transducers and new

imaging and measurement techniques.[5] High-frequency ultrasound (HFUS) and Shear-wave elastography (SWE) emerged as promising ultrasound methods to evaluate the skin involvement in patients with SSc.[5,12] HFUS is able to detect skin involvement earlier than the mRSS.[13] Even in skin apparently unaffected, HFUS and SWE were able to detect increased ultrasound-dermal thickness (DT) and stiffness in SSc patients, respectively.[13,14,15] In addition, HFUS can identify an oedematous phase in patients scoring mRSS of 0, which is useful to detect skin involvement in very early disease.[5,7] Important positive correlations between HFUS ultrasound-DT and microangiopathy, accessed by NVC, in SSc patients has already been reported.[16,17] In addition, a 5-year follow-up study demonstrated the ability of SWE to detect slight variations in skin stiffness overtime, that were not captured by mRSS.[5]

However, until now, both ultrasound methods have been only applied to patients with a definite SSc diagnosis.[5] No previous studies have evaluated the ultrasound skin measures in patients with UCTD-risk-SSc and their ability to serve early diagnosis or prognosis.

The aim of this study was to further explore the potential of HFUS and SWE as a non-invasive tool to assess skin involvement in UCTD-risk-SSc. In particular, we have compared ultrasound-DT and skin stiffness using HFUS and SWE, in 40 UCTD-risk-SSc patients and 40 healthy controls.

METHODS

Study design

This is a cross-sectional observational study approved by the Ethical Review Board at Centro Hospitalar e Universitário de Coimbra (CHUC-033-18). All participants provided informed written consent before the start of study procedures.

Population

Forty consecutive patients attending the Scleroderma Outpatient Clinic at our Rheumatology Department (Coimbra, Portugal) participated in the study. All participants fulfilled the Le Roy EC Criteria for early SSc.[18] The exclusion criteria for the patient group were: having any diagnosis of other skin disorder and/or overlap with other inflammatory rheumatic diseases.

Forty age- and gender-matched controls were also recruited from patient's family members and hospital staff. The exclusion criteria for this group were: pregnancy, diagnosis of any skin disease, connective tissue disease or rheumatic inflammatory disease, past history of cancer chemotherapeutic treatment, history of exposure to organic solvents, current or recent (<4 weeks) treatment with glucocorticoid, and past history of glucocorticoid treatment for more than 4 months, whatever the reason.

Data collection

Patients' demographic, clinical and disease characteristics

In all patients, a medical history and a clinical examination was performed. Autoimmunity and capillaroscopy data were also collected.

Nailfold videocapillaroscopy

All patients had been submitted to a NVC to evaluate and classify the microvascular damage into three stages: early, active or late.[19]

Skin-ultrasound measures

All measures were performed before noon (between 8:30 and 12:30) in the same room at a temperature between 21º and 23ºC, and after an acclimatization period of 15 minutes, with the patient lying in a supine and relaxed position. Each set of measurements took approximately 20 minutes.

Ultrasound evaluation was performed at the 17 sites of the mRSS, as follows: face (2 points, mean), chest (between sternal angle and notch), upper arm (anterior aspect, 10 cm proximal to the medial epicondyle), forearm (anterior aspect, 3 cm proximal of the wrist), hand dorsum (index/middle metacarpal interspace, 2cm proximal to the MCF joints), finger (dorsal aspect of the mid portion of the proximal phalanx of the right second finger), abdomen (10 cm distal to the sternum); thigh (10 cm proximal to the patella), leg (10 cm proximal to the lateral malleolus), and foot (first web space 2 cm proximal to the MTF joints).[20]

Skin ultrasound was performed using a Siemens ACUSON S2000 Ultrasound System HELX Evolution.

Ultrasound-dermal thickness

B-mode ultrasound was performed using an 18 MHz linear probe. A high-frequency probe offers considerably good resolution, allowing the distinction between the epidermis, dermis and subcutaneous layers of skin.[20] In particular, DT was measured on the B-mode image by an electronic caliper included in a dedicated software, identifying the upper surface epidermis-dermis and the lower layer dermis-subcutis. The value for each skin site scanned was calculated as the mean of three measurements per site, in millimetres (mm).

The same operator (TS) performed the US evaluations in all individuals, blinded to the mRSS, and recorded the relevant scans. Then, four operators (Tânia Santiago, João Lima, Catarina Gaspar and Mariana Luís) read the ultrasound scans, using an exact standardization protocol and specific software (Dicom viewer).

Ultrasound skin stiffness

Skin stiffness was measured through SWE, using virtual touch image quantification (VTIQ), using a linear 4-9 MHz transducer. The ultrasound protocol has been previously described elsewhere.[15] In brief, acceptance of an ultrasound image for analysis was based on clear visualization of an interface between the epidermis, dermis and subcutaneous tissues and on an automated image quality indicator provided by the ultrasound system. The sonographer placed sampling gates with the minimum possible size (2x2mm), over the dermis.

The VTIQ output simultaneously displays a color-coded tissue stiffness map and absolute shear-wave velocity values (in m/s, up to 10 m/s) in one single image. Higher shear-wave velocities (SWV) values indicate greater tissue stiffness. The SWV measurements were performed 3 times at each skin site, and the mean of these measurements was used for statistical analysis.

Data analysis.

Data were analysed using SPSS software, V.21 (IBM SPSS Inc., Chicago, IL, USA) with *p* values <0.05 being considered significant. Continuous variables were reported as means ± standard deviation. Categorical variables were presented as frequencies. Comparison between groups was performed using the Mann-Whitney U test or Student´s t-test, if data distribution was not normally or normally distributed, respectively.

Correlations between ultrasound-DT and stiffness at the same skin site were evaluated through Pearson correlation.

RESULTS

Demographic and clinical characteristics

The demographic and clinical characteristics of the 40 UCTD-risk-SSc patients and 40 healthy controls are presented in Table 1. In UCTD-risk-SSc and healthy controls, the mean age was 51.4 (14.9) and 49.5 (13.9), respectively. The majority were females (~93%), and ~57% in UCTD-risk-SSc and ~60% in controls had already reached menopause. Eighteen percent in UCTD-risk-SSc and 32.5% in healthy controls are or had been smokers.

The mean disease duration was 10.6 (6.6) years since RP appearance and 8.0 (5.5) years since diagnosis. RP was present in all patients. About one third of the patients were medicated with calcium channel blockers. Ten percent of the patients had a present or past history of digital ulcers. Thirteen percent belonged to Subset 1 (RP associated with capillaroscopic scleroderma pattern and positive SSc autoantibodies), and ~87% belong to Subset 2 (RP associated positive SSc antibodies and no capillaroscopic scleroderma pattern). All patients had circulating antinuclear antibodies (ANAs), 60% had Anti-centromere and 25% Anti-Scl-70 antibodies.

Ultrasound parameters

Ultrasound-DT was, on average, significantly higher in UCTD-risk-SSc patients than in controls in the dorsal face of the right and left hand (p=0.02) (Figure 1 and Table 2). In the left thigh, left leg, right and left foot, and face, ultrasound-DT was numerically and greatly higher in UCTD-risk-SSc patients, although not significantly different from controls (Table 2).

Shear-wave velocity values were significantly higher in UCTD-risk-SSc patients than in controls in the following skin sites: dorsal face right hand [1.94 (0.40) *vs* 1.61 (0.24); p=0.0001], dorsal face left hand [1.82 (0.36) *vs* 1.65 (0.25); p=0.025], right proximal phalanx [2.09 (0.60) *vs* 1.68 (0.24); p=0.001] and left proximal phalanx [2.13 (0.82) *vs* 1.66 (0.27); p=0.004] (Figure 2 and Table 3).

There were no significant correlations between ultrasound-DT and shear-wave velocity values at the same skin site (data not shown).

Table 1. Clinical parameters in UCTD-risk-SSc and healthy control groups.

	UCTD-risk-SSc (n=40)	Healthy controls (n=40)
Age, years (mean, SD)	51.4 (14.9)	49.5 (13.9)
Female (n, %)	37 (92.5)	37 (92.5)
BMI (mg/kg) (mean, SD)	24.9 (3.8)	26.8 (4.4)
Smoking status (Never/ Past and Current) (n, %)	33 (82.5) / 7 (17.5)	27 (67.5) / 13 (32.5)
Menopause status (n, %), n=37	21 (56.8)	22 (59.5)
Disease duration since Raynaud, years (mean; SD)	10.6 (6.6)	-
Disease duration since diagnosis, years (mean; SD)	8.0 (5.5)	-
Calcium channel blockers (Yes) (n; %)	13.0 (32.5)	-
Digital ulcers (yes) (n; %)	4.0 (10)	-
RP (n, %)	40 (100)	-
Subset 1 (n, %)	5 (12.5)	-
Subset 2 (n, %)	35 (87.5)	-
ANA + (n, %)	40 (100)	-
Anti-centromere + (n, %)	24 (60)	-
Anti-Scl-70 + (n, %)	6 (25)	-

Legend: ANA: Antinuclear antibodies; Ns: Non-significant; UCTD-risk-SSc: Undifferentiated Connective Tissue Disease at risk for Systemic Sclerosis; SD: Standard Deviation; RP: Raynaud´s Phenomenon; Subset 1: RP, SSc marker autoantibodies and scleroderma pattern; Subset 2: RP and SSc marker autoantibodies.

*Table 2. Ultrasound Dermal thickness **(mm)** in UCTD-risk-SSc and healthy control groups, in the 17 Rodnan skin sites.*

	UCTD-risk-SSc (n=40)	Healthy controls (n=40)	p value
Face	1.35 (0.33)	1.21 (0.38)	NS*
Chest	1.33 (0.34)	1.48 (0.41)	NS*
Abdomen	1.64 (0.39)	1.59 (0.33)	NS*
Upper Arm Right	0.77 (0.20)	0.77 (0.14)	NS*
Upper Arm Left	0.74 (0.19)	0.71 (0.13)	NS*
Forearm Right	0.83 (0.27)	0.81 (0.24)	NS
Forearm Left	0.81 (0.23)	0.81 (0.20)	NS
Dorsal face Right Hand	0.77 (0.32)	0.62 (0.12)	0.02
Dorsal face Left Hand	0.79 (0.39)	0.62 (0.13)	0.02*
Proximal phalanx right	0.64 (0.14)	0.61 (0.11)	NS
Proximal phalanx left	0.66 (0.16)	0.60 (0.09)	NS
Thigh Right	1.43 (0.27)	1.33 (0.27)	NS*
Thigh Left	1.47 (0.27)	1.32 (0.34)	NS*
Leg Right	0.99 (0.60)	0.96 (0.26)	NS
Leg Left	1.05 (0.70)	0.89 (0.26)	NS
Foot Right	0.80 (0.38)	0.66 (0.16)	NS
Foot Left	0.78 (0.36)	0.65 (0.14)	NS*

*Legend: UCTD-risk-SSc: Undifferentiated Connective Tissue Disease at risk for Systemic Sclerosis; *We performed t student parametric tests, as the variables were normally distributed. For the others values Mann-Whitney U test was performed.*

*Table 3. Shear-wave velocity values **(m/s)** in UCTD-risk-SSc and healthy control groups, in the 17 Rodnan skin sites.*

	UCTD-risk-SSc (n=40)	Healthy controls (n=40)	p value
Face	1.30 (0.18)	1.33 (0.19)	NS*
Chest	1.66 (0.49)	1.51 (0.20)	NS*
Abdomen	1.41 (0.26)	1.36(0.20)	NS
Upper Arm Right	1.33 (0.23)	1.33 (0.18)	NS*
Upper Arm Left	1.45 (0.31)	1.42 (0.23)	NS*
Forearm Right	1.42 (0.26)	1.51 (0.18)	NS*
Forearm Left	1.47 (0.31)	1.49 (0.16)	NS
Dorsal face Right Hand	1.94 (0.40)	1.61 (0.24)	0.0001*
Dorsal face Left Hand	1.82 (0.36)	1.65 (0.25)	0.025*
Proximal phalanx right	2.09 (0.60)	1.68 (0.24)	0.001
Proximal phalanx left	2.13 (0.82)	1.66 (0.27)	0.004*
Thigh Right	1.52 (0.17)	1.52 (0.15)	NS*
Thigh Left	1.49 (0.17)	1.51 (0.13)	NS*
Leg Right	1.95 (0.37)	1.91 (0.61)	NS
Leg Left	1.95 (0.26)	1.89 (0.39)	NS
Foot Right	1.63 (0.29)	1.53 (0.24)	NS*
Foot Left	1.67 (0.38)	1.56 (0.24)	NS*

*Legend: UCTD-risk-SSc: Undifferentiated Connective Tissue Disease at risk for Systemic Sclerosis; *We performed t student parametric tests, as the variables were normally distributed. For the others values Mann-Whitney U test was performed.*

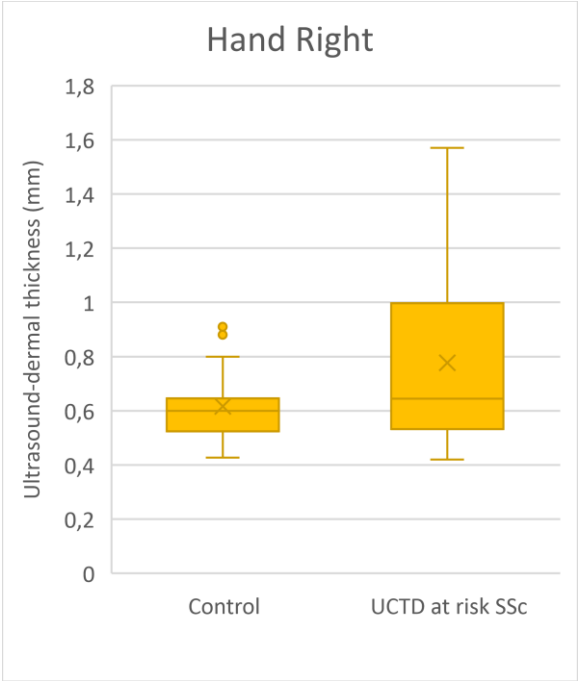

Figure 1. ***Ultrasound-DT*** *in the right hand, of patients with UCTD-risk-SSc versus controls. Box-plots (in yellow) with the mean value represented (in grey "x").*

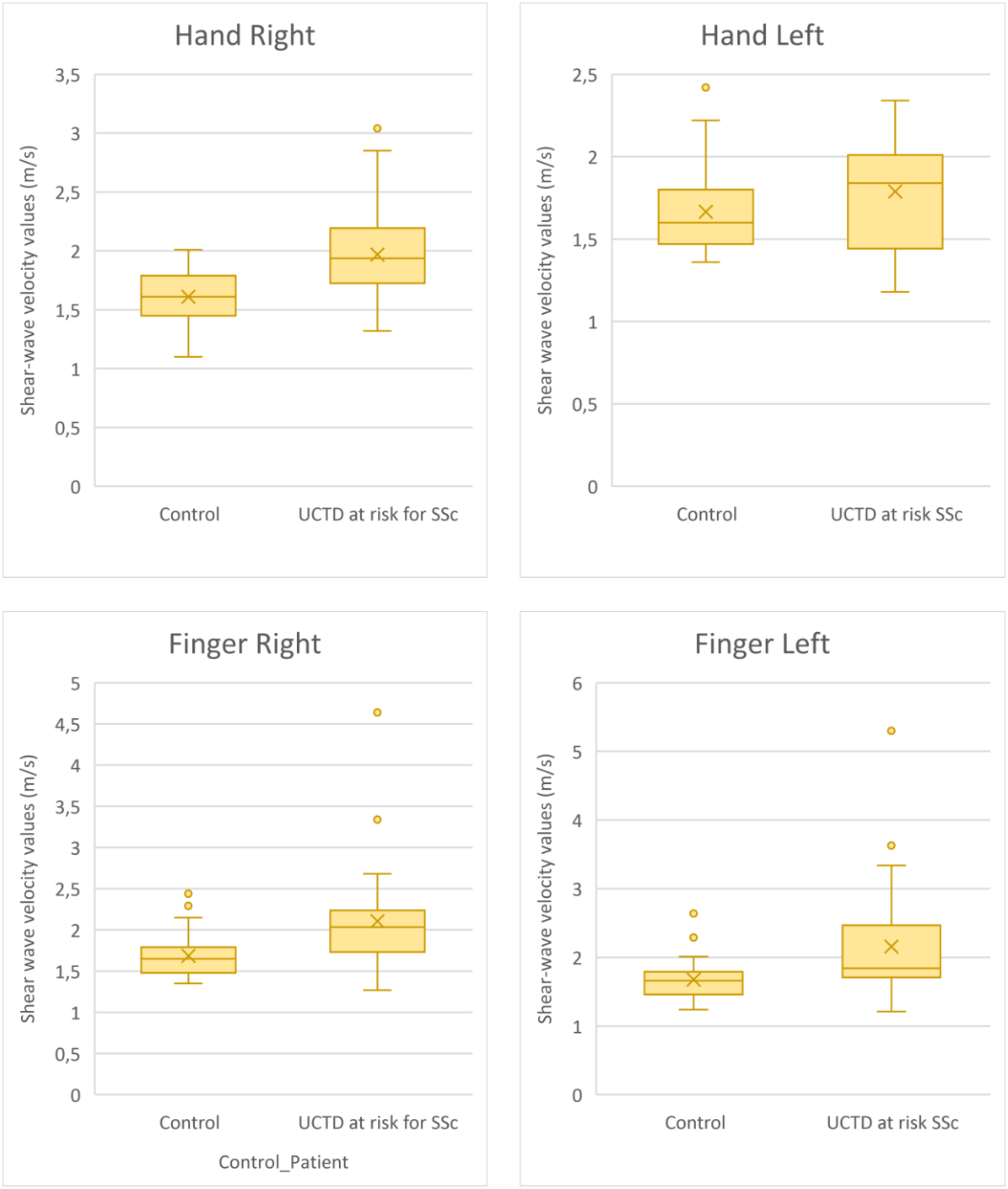

Figure 2. ***SWE velocity*** *in the right hand, left hand, right finger and left finger of patients with UCTD-risk-SSc and healthy controls. Box-plots (in yellow) with the mean value represented (in grey "x").*

DISCUSSION

To our knowledge this is the first study reporting the application of ultrasound-DT and elastography shear-wave velocity in patients with UCTD-risk-SSc.

Shear-wave velocities values were significantly higher in the hands and fingers of UCTD-risk-SSc patients than in controls, bilaterally. Also, ultrasound-DT was significantly higher in the hands in UCTD-risk-SSc patients compared with controls. There were no significant differences in the others Rodnan skin sites evaluated between UCTD-risk-SSc patients and controls. SWE identified stronger and more widespread differences between the groups, which may suggest that this ultrasound method may have higher sensitivity to detect subtle skin changes than HFUS.

The skin ultrasound findings observed in the hands and fingers of these patients seem to reflect subclinical skin involvement. Previous studies have demonstrated that HFUS and SWE can detect increased dermal thickness and stiffness in skin from SSc sites considered clinically unaffected.[13-15] Interestingly, we found that significantly differences in ultrasound-DT and skin stiffness occur in skin areas that are more frequently involved in early stages of the disease.[21] It seems plausible that the above-mentioned skin changes may be related to their long history of RP (mean duration of 10.6 (6.6) years). This may induce microangiopathy in the rich microvascular network located in the dermal layer, and result in interstitial edema and changes in the local skin properties. [19,22]

Our results need to be evaluated in the light of some study limitations. It is obvious the small sample size in the UCTD-at-risk-SSc/Subset 1 (RP associated with capillaroscopic scleroderma pattern and positive SSc autoantibodies) with only five out 40 patients. This is, in fact, the most promising subset due to its higher probability of evolving to definite SSc. Also, being a cross-sectional study, it does not allow inferences about the progression of the clinical profile of these patients. Lastly, the transducer with low frequency (eg, 9Mhz) used in the SWE provides a low resolution of the superficial skin layers.

In conclusion, our findings provide the first evidence suggesting that HFUS and SWE can differentiate patients with UCTD-risk-SSc from healthy controls, in particular, at the hands and

fingers, suggesting that both methods are able to identify early skin changes in UCTD-risk-SSc. Further prospective studies including a larger number of patients with the different subsets of UCTD-risk-SSc, namely subset 1, are required to understand if these ultrasound measures may help to predict progress to definitive SSc and, thus, allow early preventive interventions.

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I thank my dear Iolanda, my colleagues, and specially my parents for their unconditional support during these 6 years of medical school.

FINAL NOTES:

The Abstract of this thesis has been submitted to 2021 European League Against Rheumatism congress. (Please See Appendix I and II).

My role in this project was to collect patient's demographic and clinical characteristics, read and evaluate the ultrasound images and write this manuscript, under the orientation of MD Tânia Santiago and PHD, MD José António Pereira da Silva. I and my colleague, Catarina Gaspar, have had training sessions to read and evaluate the skin ultrasound images (~3hours total), led by MD Tânia Santiago.

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APPENDIX

Appendix I: Submission to 2021 EULAR congress notification

Abstract submission notification

Dear João Lima,

Thank you for your submitting your abstract to **EULAR 2021 Congress.**

Details of your abstract

Number:	3384
Title:	Ultrasound assessment of dermal thickness and stiffness in undifferentiated connective tissue disease at risk for systemic sclerosis
Presenting Author:	MD Tânia Santiago
Authors: Tânia Santiago	Centro Hospitalar e Universitário de Coimbra; Centro Hospitalar e Universitário de Coimbra; Rheumatology
Authors: Mariana Luis	Centro Hospitalar e Universitário de Coimbra; Centro Hospitalar Universitário de Coimbra; Rheumatology
Authors: João Lima	Institute for Clinical and Biomedical Research (iCBR)
Authors: Catarina Gaspar	xx
Authors: Maria Joao Salvador	Centro Hospitalar e Universitário de Coimbra
Authors: José Antonio P. da Silva	Centro Hospitalar e Universitário de Coimbra; Centro Hospitalar e Universitário de Coimbra; Rheumatology

Appendix II: Abstract Submitted to 2021 EULAR congress

Ultrasound assessment of dermal thickness and stiffness in undifferentiated connective tissue disease at risk for systemic sclerosis

Tânia Santiago[1,2], Mariana Luís[1,2], João Lima[2], Catarina Gaspar[2], MJ Salvador[1,2], JAP da Silva[1,2].

1- Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

2- Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal.

Background: High-frequency ultrasound (HFUS) and shear-wave elastography (SWE) allow an objective assessment of skin involvement in systemic sclerosis (SSc) patients.[1] Till now it has been applied to patients with established diagnosis.[2,3] However, there is no data concerning its application in Undifferentiated Connective Tissue Disease at risk for SSc (UCTD-risk-SSc), i.e., patients with Raynaud's phenomenon and either SSc marker autoantibodies or typical capillaroscopic findings or both, not satisfying classification criteria for SSc.[4] Our aim was to compare ultrasound-dermal thickness (DT) and skin stiffness using high-frequency ultrasound and shear-wave elastography, in UCTD-risk-SSc and healthy controls.

Methods: Forty UCTD-risk-SSc patients and 40 age- and gender-matched healthy controls were included. Ultrasound-DT was measured using a 18MHz probe, and skin stiffness (i.e. shear-wave velocity values, SWV) using the VTIQ software with a 9MHz probe, at the 17 Rodnan skin sites. Continuous data were expressed as the mean (SD), and Mann-Whitney U test was performed to compare differences between the groups as variables were not normally distributed. Associations between variables were analyzed using the Spearman's correlation.

Results: SWV values were significantly higher in patients with UCTD-risk-SSc compared with controls at the right and left hands, and in the right and left fingers (table 1). Higher values of ultrasound dermal-thickness were found in the fingers and hands bilaterally, although differences were only significantly at the hands, compared with healthy controls (table 1). There were no significant differences in the other Rodnan skin sites. There was no significant correlation between ultrasound-dermal thickness and stiffness at the same skin site.

Conclusions: This study provides the first evidence suggesting that ultrasound-DT and stiffness can discriminate patients with UCTD-risk-SSc from healthy controls. Prospective studies including a larger number of patients with different subsets of UCTD-risk-SSc are needed to investigate diagnostic and prognostic value of the ultrasound parameters in this group.

Table 1. Clinical and ultrasound parameters in UCTD-risk-SSc and healthy control groups.

	UCTD-risk-SSc (n=40)	**Healthy controls (n=40)**	**p value**
Age, mean (SD)	51.4 (14.9)	49.8 (13.9)	Ns
Female, n (%)	36	36	
Raynaud phenomenon, %	100.0%	-	
ANAs Anti-centromere, % Anti-Scl70+, %	100.0 60.0 11.5	-	
Scleroderma/non-scleroderma pattern in capillaroscopy, %	5.0/95.0	-	-
Ultrasound parameters			
Dermal thickness (mm)			
Dorsal hand Right	0.77 (0.32)	0.62 (0.12)	0.02
Dorsal hand Left	0.79 (0.39)	0.62 (0.13)	0.02
Proximal phalanx right	0.64 (0.14)	0.61 (0.11)	Ns
Proximal phalanx left	0.66 (0.16)	0.60 (0.09)	Ns
SWV values (m/s)			
Dorsal hand Right	1.94 (0.40)	1.61 (0.24)	0.0001
Dorsal hand Left	1.82 (0.36)	1.65 (0.25)	0.025
Proximal phalanx right	2.09 (0.60)	1.68 (0.24)	0.001
Proximal phalanx left	2.13 (0.82)	1.66 (0.27)	0.004

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