

## Developing a quantitative tool to evaluate dermal fibrosis in systemic sclerosis patients: a case-control study

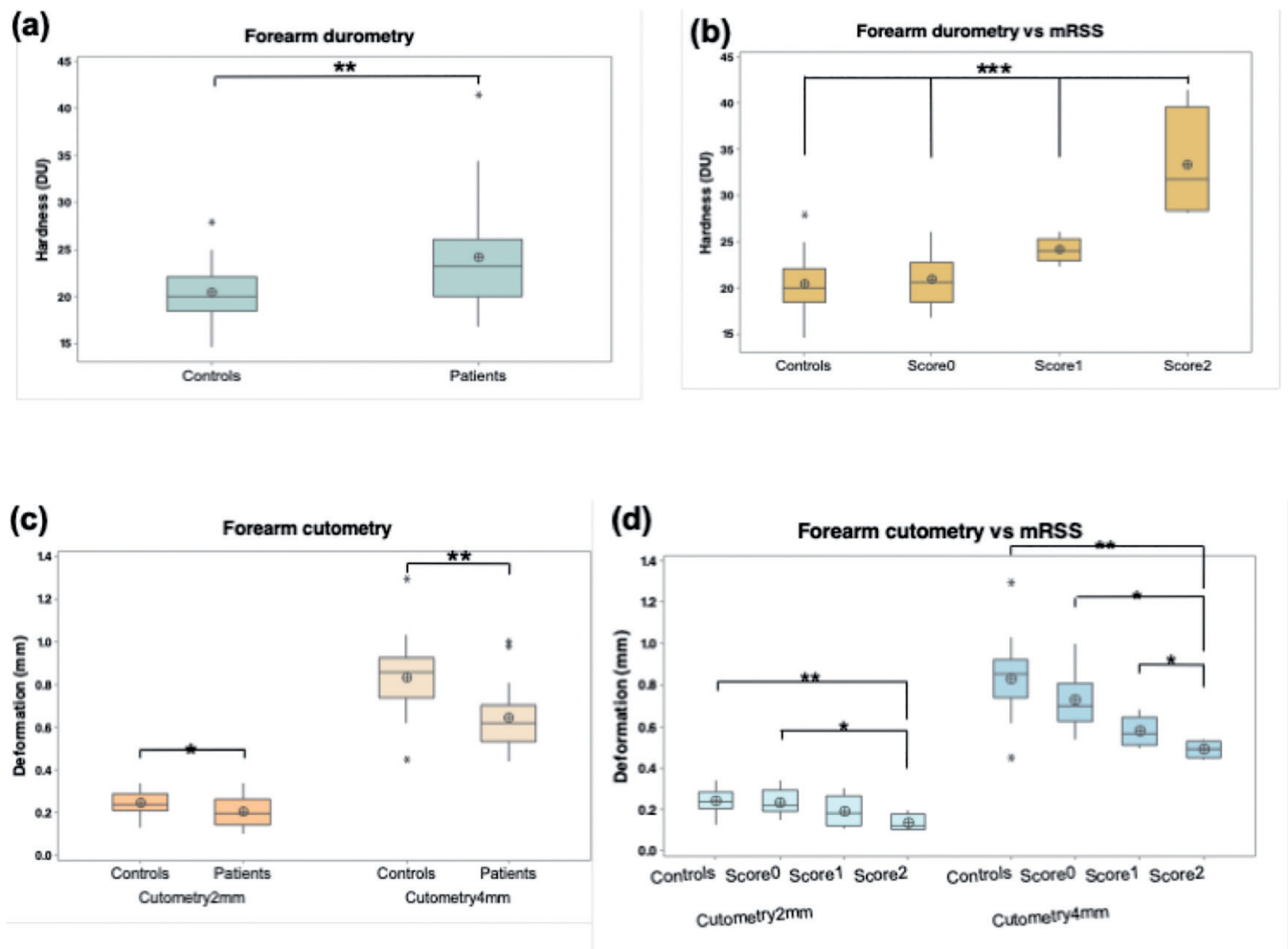
Sirs,

Systemic sclerosis (SSc) is an autoimmune compound multisystem condition with heterogeneous clinical manifestations (1-5). The skin thickening or fibrosis associated with SSc is generated by the formation of intercellular matrix in the dermis layer of the skin, by the accumulation of collagen, and by the affiliated oedema, owing to inflammation and microvascular damage (1-5). Currently the modified Rodnan Skin Score (mRSS) is the accepted measure by which we assess the extent of SSc skin fibrosis (6). The mRSS score assesses the thickness of skin, which is significant in the evaluation of SSc, but hardness and firmness of the skin are two separate characteristics, with a

possible high impact in SSc disease's merit quantification and process (1-5). In addition, with the possible use of "more intelligent technology" machines, subjectivity will lessen and reliability will rise. The purpose of mRSS is to assess skin thickness and not other skin changes of the patient, such as tethering and hardness. Hence, we aimed to investigate alternative methods for assessing skin fibrosis in SSc patients. Durometry is a painless, non-invasive, method to assess skin hardness. Skin thickness, elasticity, density and oedema can affect skin hardness. Moreover, it offers a wider range of values for the evaluation of skin disease, as mRSS limits the scoring to only four different options. The broadened range, as well as the scaling, can make the assessment more precise as minor or moderate skin changes will be detected. Added to that, there is less variation of the durometry results measured by different investigators, thus making the assessment more objective (6).

Cutometry measures the skin's viscoelastic properties, by using the suction method. It is a non-invasive method appropriate for quantitative and objective evaluation of skin alterations, owing to SSc. The escalated skin viscoelasticity could be proposed as a new indication for the very early diagnosis of SSc (7), so cutometry could be an additional tool to the mRSS. Besides that, inter-observer intra-class correlation is significantly higher for cutometry rather than for the mRSS (8).

The goal of this preliminary study was to investigate the validity and reliability of durometry and cutometry in the discrimination of patients from healthy population, serving as diagnostic and prognostic tools in the assessment of SSc. The study comprised of twenty female healthy controls (48.3±12.2 years) and twenty female patients (53.5±12.8 years). All patients had diffuse scleroderma with an average duration of 5 years (range 3-7).



**Fig. 1.** Box-and-whisker plot (box: interquartile range, +: mean; —: median; \*:  $p \leq 0.05$ ; \*\*:  $p \leq 0.01$ ; \*\*\*:  $p \leq 0.001$ ), depicting: (a) statistical significant difference in forearm hardness ( $p=0.0015$ ) between controls and patients; (b) remarkable correlation of durometry and mRSS for patients with moderate fibrosis, discriminating them from the controls, and from the patients with mild or no fibrosis ( $p < 0.001$ ); (c) statistical significant difference in forearm firmness between controls and patients, using cutometry's 2mm probe ( $p=0.049$ ) and 4mm probe ( $p=0.01$ ); (d) notable correlation of cutometry and mRSS for patients with moderate fibrosis; the 2mm probe discriminated them from the controls ( $p=0.007$ ) and from the patients without fibrotic activity ( $p=0.029$ ); the 4mm probe discriminated the moderately thickened patients from the controls ( $p=0.002$ ), from the patients with mild fibrosis ( $p=0.013$ ), and from the patients without fibrotic activity ( $p=0.026$ ).

The forearm site was selected as it a region evaluated in the literature for drug testing, easily accessible and would not causing any irritation to the patient. Durometry measurements were made at predetermined landmark sites in the dorsal sites of the forearms, in the middle line and with a distance of 6 cm from the elbow crease. For cutometry measurements, the diameter of the probe that was used, 2 mm and 4 mm, refers to the aperture diameter of each probe, that the negative pressure is applied to the skin.

The results implement accuracy of durometry and cutometry to identify SSc patients. In terms of hardness, the results of this study suggest that there is a significant difference between the controls and the patients (mean value 20.42 *versus* 24.18, and  $p=0.015$ ) (Fig. 1a). In terms of deformation, that represents skin firmness, the results suggest a significant difference between the controls and the patients, in regards to the 2 mm probe ( $p=0.049$ ), and to the 4mm one ( $p=0.01$ ). In terms of hardness, the results of this study suggest that the correlation between durometry and mRSS score is significant as the mean for the moderately thickened patients (score 2) was widely discriminated from the rest categories (Fig. 1b). In terms of deformation, that is representative of skin firmness, the results suggest that the correlation between the cutometry (using the 2 mm and the 4 mm probe) and mRSS was significant as the mean for moderately thickened pa-

tients (score 2) was extensively differentiated from the controls and the uninvolved patients. It is important to highlight that the durometry and cutometry were able to distinguish between severity of fibrosis in this cohort of patients (Fig. 1b and d). Further work will understand the role of these non-invasive techniques in the detection of early scleroderma and monitoring disease progression a large cohort of patients. To conclude, quantitative assessment tools are reliable for monitoring the severity of skin fibrosis in patients with SSc.

I. GIANNAKOPOULOS<sup>1,4</sup>, MD  
M.F. GRIFFIN<sup>1,4</sup>, MBChB, MSc, MRes, MRCS, PhD  
C.P. DENTON<sup>1,4</sup>, PhD, FRCP  
P.E.M. BUTLER<sup>1,4</sup>, MD, FRCSI, FRCS, FRCS(Plast)

<sup>1</sup>Charles Wolfson Centre for Reconstructive Surgery, Royal Free Hospital, London;  
<sup>2</sup>UCL Centre for Nanotechnology and Regenerative Medicine, Division of Surgery & Interventional Science, University College London; <sup>3</sup>Centre for Rheumatology, Royal Free Hospital, London; <sup>4</sup>Plastic & Reconstructive Surgery, Royal Free Hospital, London, UK.

Please address correspondence to:  
Michelle Griffin,  
Royal Free Hospital,  
Pond Street,  
London NW3 2QG, United Kingdom.  
E-mail: 12michellegriffin@gmail.com

Competing interests: none declared.

© Copyright CLINICAL AND  
EXPERIMENTAL RHEUMATOLOGY 2020.

## References

1. ELHAI M, AVOUAC J, KAHAN A, ALLANORE Y: Systemic sclerosis: Recent insights. *Joint Bone Spine* 2015; 82: 148-53.
2. STERN EP, DENTON CP: The pathogenesis of systemic sclerosis. *Rheum Dis Clin North Am* 2015; 41: 367-82.
3. BRADY SM, SHAPIRO L, MOUSA SA: Current and future direction in the management of scleroderma. *Arch Dermatol Res* 2016; 308: 461-71.
4. HO YY, LAGARES D, TAGER AM, KAPOOR M: Fibrosis—a lethal component of systemic sclerosis. *Nat Rev Rheumatol* 2014; 10: 390.
5. RUDNICKA L, VARGA J, CHRISTIANO AM, LOZARV, JIMENZA SA, UITTO J: Elevated expression of type VII collagen in the skin of patients with systemic sclerosis. Regulation by transforming growth factor-beta. *J Clin Invest* 1994; 93: 1709-15.
6. MERKEL PA, SILLIMAN NP, DENTON CP *et al.*: Validity, reliability, and feasibility of durometer measurements of scleroderma skin disease in a multicenter treatment trial. *Arthritis Rheum* 2008; 59: 699-705.
7. ENOMOTO DN, MEKKES JR, BOSSUYT PM, HOEKZEMA R, BOS JD: Quantification of cutaneous sclerosis with a skin elasticity meter in patients with generalized scleroderma. *J Am Acad Dermatol* 1996; 35: 381-7.
8. POPE JE, BARON M, BELLAMY N *et al.*: Variability of skin scores and clinical measurements in scleroderma. *J Rheumatol* 1995; 22: 1271-6.