Viewpoint on:

The role of skin ultrasound in systemic sclerosis: looking below the surface to understand disease evolution

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Summary

Skin ultrasound (US) showed promising results in the evaluation of skin involvement in systemic sclerosis (SSc) patients, as recently confirmed by the systematic literature review from the World Scleroderma Foundation Skin Ultrasound Group. The current viewpoint will discuss the role of skin US in the evaluation of skin involvement in SSc patients. In particular, it will highlights the possibility to detect an early sub-clinical skin involvement from the very early phase of SSc suggesting its possible use in the diagnosis and follow-up of the disease. To detect subclinical skin involvement, the comparison of the results of SSc skin US versus the skin of healthy controls is mandatory to define what is affected and what is spared in the skin layers. The potential of this non-invasive technique may suggest its future role both in clinical practice and in randomised clinical trials (RCTs), potentially replacing an invasive and painful procedure as skin biopsy and also playing an important role in retention of patients during RCTs.

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Main document

In systemic sclerosis (SSc), the skin is the cardinal target of the disease, and its involvement is progressively characterised by an oedematous, a fibrotic and an atrophic phase. The progression of skin disease has major clinical and prognostic relevance being linked to a more severe disease (e.g., development of major organ-based complications and mortality) and related to disability with a great impact on patients' quality of life.

Assessment of skin involvement in SSc has frequently been used as the primary outcome measure of treatment efficacy in randomised clinical trials (RCTs) [1, 2]. Skin thickness is almost universally scored (e.g., in RCTs) using the modified Rodnan skin score (mRSS): a semiquantitative measure of cutaneous involvement that can only very indirectly be an assessment of "thickness" of the skin due to its limitations. Among these, mRSS is ~~a subjective measurement~~ burdened by a high inter-observer variability [3, 4] and limited discrimination of subtle change within an integer score compared to a directly visualised continuous measure of skin thickness [3]. In addition, it seems unable to distinguish between oedema and fibrosis, and it is considered a valid examination only in the evaluation of skin involvement in the diffuse subset of the disease (dcSSc). Conversely in the limited cutaneous one (lcSSc), mRSS seems to be scarcely sensitive to change [3]. Therefore, a significant interest has been focussed on alternative assessment of skin thickness. Among these, skin ultrasound (US) is now considered as an attractive quantitative measurement tool which might provide objective measurement of skin thickness in SSc [5].

The purpose of this viewpoint is to focus on the *emerging role* of US in the evaluation of SSc skin involvement clinically and in clinical research, the *need of standardization*, and on the emerging importance of the US evaluation of the *hypodermis*. We will also address a possible role in the very early subclinical phase of SSc, helping to better understand the disease process and potentially replacing the skin biopsy in this circumstance. This would be of paramount importance for patients, as an invasive and painful procedure could be replaced by a non-invasive, painless and non-harmful examination, potentially leading to similar results. For this reason, instead of biopsy, skin US could also play an important role in retention of patients during RCTs. In addition, compared to skin biopsy, US may allow the contemporary assessment of different skin sites and likely has a lower cost.

Recently, the World Scleroderma Foundation (WSF) Skin Ultrasound Group completed a systematic literature review confirming the growing interest of skin US and its emerging role in the measurement of skin thickness in SSc [6]. It also provided valuable practical information: details on the equipment, settings, standardized images, scoring systems, skin sites to be examined, and potential contribution of elastography [6]. Consequently, the WSF working group highlighted the *lack of a standardized US procedure and its lack of full validation.* The working group also produced five overarching principles and seven recommendations for the execution and reporting of skin ultrasound studies in SSc [7]. The authors specified the characteristics of the probe (high-frequency linear probe, ≥18mHz), and its correct positioning during the US examination. In addition, although US has not been yet standardized, the need of appropriate training of examiners was indicated to reduce variability and ensure the quality of the examination. Furthermore, it was recommended that the US evaluation of skin involvement should follow the European Alliance of Associations for Rheumatology (EULAR) task force recommendations (23 items, 21 mandatory and 2 optional) for reporting US procedures in rheumatic and musculoskeletal diseases [8].

On top of these recent findings, US offers several additional challenges. Indeed, it is still unclear whether and how to measure the various cutaneous layers in SSc [7], thus leaving an unmet need still to be addressed by a careful research agenda. Previously, studies have reported that skin US could detect subclinical dermal involvement in areas with a normal mRSS [9, 10]. Naredo et al reported a novel observation using an ultra-high-frequency US probe (50-70 MHz) on oedematous puffy fingers, describing a significant increase of the hypodermis thickening, that was strikingly increased in comparison to healthy controls [11]. This unexpected finding could suggest a possible role of skin US also in the evaluation of subclinical skin involvement in the *very early* phase of the disease, when the attention should therefore move from the dermis (classically considered the skin layer where the disease develops) to the hypodermal layer. This finding both supports the use of the US to discriminate the involvement of the different skin layers throughput the whole disease course from the early oedematous, to the fibrotic and to the later atrophic phases and could decipher the early pathogenic events of skin involvement in SSc. The WSF taskforce has identified which layer to measure as an unmet need and as one of the main issues to be addressed in the future research agenda [6, 7].

In the early phase of the disease, interstitial oedema has been widely described reflecting the perivascular homing of inflammatory cells due to microvascular angiopathy, and dysfunction of deeper lymphatic collector vessels [12]. Puffy fingers are considered the clinical sign of interstitial

hypodermal oedema and their role in the prediction of SSc development in patients with Raynaud's phenomenon and antinuclear antibodies positivity has been recently confirmed in the VEDOSS study [13]. In puffy fingers, interstitial oedema is clinically evident, and also detectable through capillaroscopy which identifies giant capillaries with a fluffy appearance due to the fluid extravasation [12]. Taken together, this evidence clearly testifies to the ongoing leaking process in the inflamed tissues within SSc fingers. Therefore, the parallel US finding of increased hypodermal thickness may reflect the interstitial oedema which characterises the early phase of the disease due to vascular leak consequent to endothelium disease and probably associated to lymphatic microangiopathy [14, 15]. This detail is of pivotal importance as it addresses the fact that US may disclose the condition and involvement of the different cutaneous layers (dermis and hypodermis) in the different phases of the evolution of SSc skin involvement (Figure 1). In addition, US also may show the articular and periarticular involvement from the early phase of the disease, and detect the modification of the tenosynovial structures even identifying enthesopathy in SSc patients [16, 5]. In more advanced phases, when the disease progresses to fibrosis, and eventually to atrophy, the dermis seems to be more prominently thickened and the difference between dermal layers is finally lost in the late atrophic shrinking phase [17].

Therefore, the recognition of the ~~real~~ status of the skin layers by US in the different SSc phases may represent an inflection point in the evaluation of the disease. Indeed, US might allow the *objective* measurement of skin disease activity and progression, as well as response to treatment. This possibility may open new avenues for US as a *skin outcome measure* in RCTs as a potential alternative to the mRSS also for the reported good inter-observer reliability of skin US [18, 19].

To facilitate future clinical trials and practice, US ~~will~~ have to fulfil the OMERACT filters of criterion, content and construct validity, ~~reproducibility,~~ reliability, responsiveness, ~~and~~ discrimination and feasibility [20]. Moreover, skin US must be standardized so there is uniformity for the sites to be evaluated, the skin layers to be examined, the number of images to be analysed at each site, the scoring system and the equipment to use. In SSc, the objective measurement of skin US values in comparison to healthy controls may allow both the identification of the earliest and often subclinical US signs of skin involvement and the detection of minimal changes also in the lcSSc subset, thus meeting the still open patients' unmet needs of early diagnosis. In this context, Santiago T et al recently reported preliminary gender- and age-specific normal percentile ~~normal~~ reference curves for ~~and~~ ultrasound–dermal thickness in each Rodnan site ~~percentile curve in females and in males in six sites~~ [21]. Therefore, the comparison of the results of SSc skin US versus the skin of healthy

controls is now mandatory in order to identify the gold standard as a reference to define what is affected and what is spared in the skin layers. Beyond that, US could be performed ~~administered~~ several times, centrally analysed if requested and compared throughout time without the scepticism of patients in undergoing a very painful test which would not give any relevant additional information. The health care costs of this procedure remain to be estimated as already mentioned in the research agenda of the WSF working group recommendations that questioned about the feasibility of skin US, in particular its cost in equipment and software and in time taken for image acquisition and analysis [7].

In addition, the diagnostic capacity of defining the cut-off values for the measurement of skin thickness may also assist the clinician to recognize, at any time of the disease progression, the condition of the involved skin layers, even when no clinical signs of skin involvement are evident. Furthermore, late skin involvement (>5 years), including the progression from the limited involvement of the extremities to a diffuse subset of the disease has been recently recognised [22, 23]. For example, in a study from the EUSTAR cohort, one-fifth of SSc patients experienced mRSS worsening after five years disease duration (usually due to new worsening or failure of the skin to improve) [23].

Finally, in the future, research should be focused on the correlation of skin US with pathological specimens (e.g., skin biopsies) -called criterion validity- to precisely define the degree to which skin US can describe and characterize biological events taking place within the different cutaneous layers (from dermis to hypodermis) over time [24, 19]. Recent studies opened the perspective of a "precision medicine" in SSc through the evaluation of molecular signatures in skin biopsies leading to the identification of specific disease subsets that may drive the therapy choice [25].

As above mentioned, skin US may detect subclinical changes from the earlier phases of the disease with the potential to replace skin biopsy. In this context, in the future the possibility to relate US findings to molecular signatures may represent the next effort to be made to predict skin and disease trajectories through a non-invasive and reproducible method as skin US. This challenging scenario suggests the potential for a new role of skin US in RCTs and in clinical practice, with a "precision medicine" perspective. To achieve this task, an international collaboration is mandatory to eventually incorporate skin US in routine practice and research -including RCTs- to objectively measure and evaluate (monitor progression) skin involvement and thickness, respectively, in the different phases of the disease as well as to find its place in documenting treatment effects. To detect subclinical involvement in the earlier phases through US skin could indicate the possibility to

identify subclinical changes in dermal or hypodermal layers during the follow-up of SSc patients demonstrating the sensitivity to change of this examination and encouraging its use in RCTs. The meaning of this subclinical changes and their impact as measure of outcome and their correlation with functioning, and/or survival of SSc patients still remains to be evaluated.

In conclusion, in SSc skin US represents a technique in the evaluation of skin involvement which may be important in determining the stage of disease, understanding new aspects of pathogenesis and defining treatment effects without using invasive and painful procedures. However, further work is urgently needed to standardize the US procedure so it can be used among multiple centers and for the evaluation of the cutaneous layers to demonstrate its validity, reproducibility, sensitivity to change and discrimination in this circumstance. Furthermore, content validity and sensitivity to change still remain to be demonstrated. For this purpose, an international collaboration will be crucial to fulfil the OMERACT validation filters and inform future adoption of skin US in clinical practice and clinical research.

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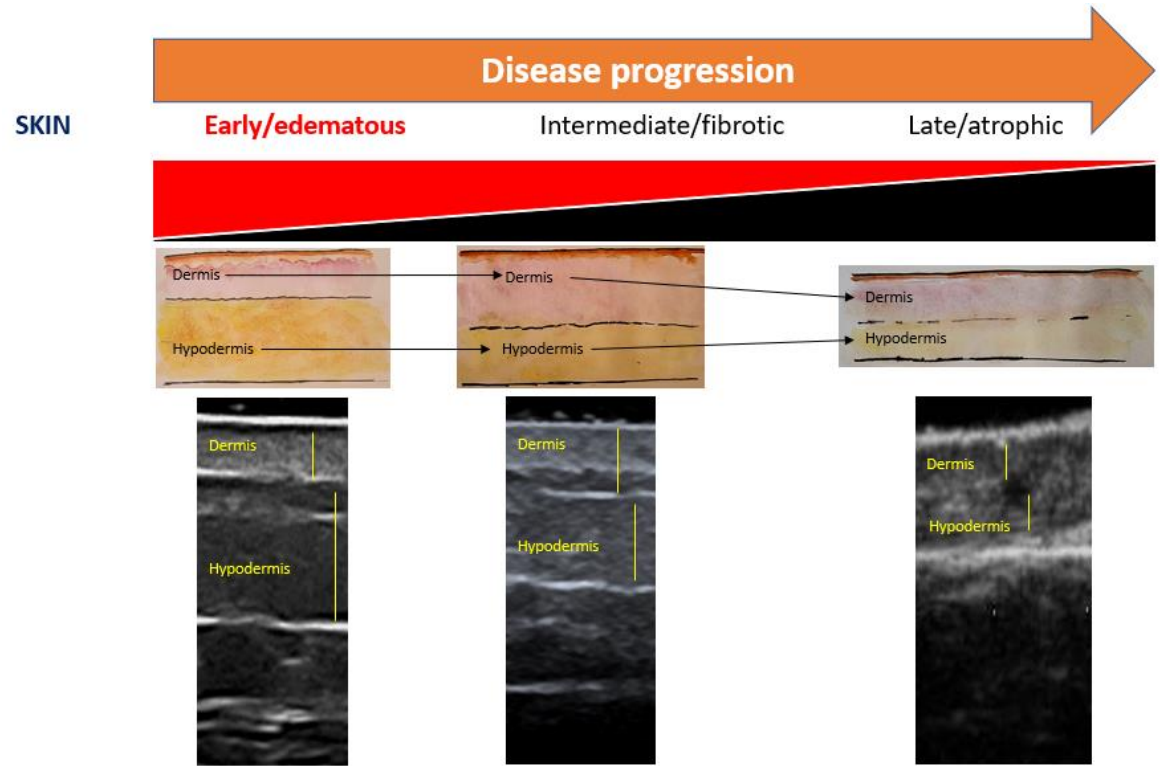
Figure 1. Skin involvement during the three disease's phases



The figure schematically represents major cutaneous structures alterations during the disease progression. In the edematous phase an increase in hypodermis thickness is predominant, followed by a subsequent increase also in dermis thickness in the fibrotic phase of the disease. In the last atrophic phase, both dermis and hypodermis decrease in thickness

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