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Should all digital ulcers be included in future clinical trials of systemic sclerosis-related digital vasculopathy?

Michael Hughes[a,*], Andrea Murray[a,b], Christopher P. Denton[c], Ariane L. Herrick[a,d]

[a] Centre for Musculoskeletal Research, The University of Manchester, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
[b] Photon Science Institute, The University of Manchester, UK
[c] Centre for Rheumatology and Connective Tissue Diseases, Royal Free Hospital, London, UK
[d] NIHR Manchester Biomedical Research Centre, Central Manchester NHS Foundation Trust, Manchester Academic Health Science Centre, UK

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ABSTRACT

Digital ulcers (DU) are a common manifestation of systemic sclerosis (SSc) and occur at a variety of locations including the fingertips and over the extensor aspects of the hands. However, most recent clinical trials have included only fingertip DUs as these are believed to be ischaemic in aetiology, and therefore likely to benefit from treatment with vasoactive drug therapies. There is an emerging evidence base to suggest that all DUs in SSc could share an ischaemic component which is potentially responsive to vascular therapy. Our hypothesis is that is that DUs occurring at sites other than the fingertips, in particular, those overlying the extensor aspect of the hands, may also have a potentially reversible ischaemic component. We review the evidence under the headings: 'microvascular imaging', 'structural microvascular' and, 'functional vascular disease', 'macrovascular involvement' and 'vascular associates'. Based upon the current evidence, we would encourage the expert SSc community to reconsider the rationale for including only fingertip DUs in future SSc clinical trials, and suggest an agenda for future research.

Introduction

Systemic sclerosis (SSc) is an uncommon, complex autoimmune rheumatic disease characterised by a progressive systemic vasculopathy, irreversible fibrosis of the skin and other internal organs, and activation of the immune system [1,2].

Digital ulcers (DUs) are common in patients with SSc and are responsible for much of the pain and disability associated with the disease. Around half of patients with SSc report a history of DUs, often occurring occur early in course of the disease [3–8]. DUs are associated with significant hand and global disability, impacting negatively on the activities of daily living, including occupation [9,10]. In addition, in patients with SSc, a history of DUs (compared to without) at presentation has also been reported to be predictive of a worse disease course (including cardiovascular disease and death) [11].

DUs commonly occur on the fingertip and over the extensor aspects of the hands, particularly overlying the small joints of the hands. Amanzi et al [12] reported that (out of 792 DUs) fingertip DUs were commoner than extensor DUs (55% vs 31%). Whereas, in a prospective study over 12 months, the prevalence of both fingertip and extensor DUs was 6%, and both types of DU were equally disabling [9]. DUs can also less commonly occur at other sites of the hands, including at the base of the nail and on the lateral aspects of the digits. DUs can also occur in relation to underlying subcutaneous calcinosis (the subcutaneous or intracutaneous deposition of calcium salts). Fig. 1 depicts a range of DUs in patients with SSc.

Despite current treatments to both prevent (e.g. endothelial receptor-1 antagonists and phosphodiesterase type-5 inhibitors) [13,14] and treat DUs [15], recurrent DUs remain a major clinical burden in many patients with SSc. Recent prospective (collected over two years) data from the DUO (Digital Ulcer Outcome) registry revealed that over half of patients with SSc had either 'recurrent' DUs (more than 2 episodes) or 'chronic' DUs (present at every clinic visit) (46.2% and 11.2%, respectively) [16].

At present, only fingertip DUs are generally believed to be ischaemic in aetiology, whereas, extensor aspect DUs are thought to occur primarily due to recurrent microtrauma and increased skin tension from tissue fibrosis, often occurring at sites of joint contracture. Little (if anything) is known about the pathophysiology of SSc-DUs which occur at other sites of the hands. Furthermore, it has been postulated that the development of calcinosis could be related to SSc-related microangiopathy [17], and ischaemia could also be implicated in the development of calcinosis-associated DUs.

As the pathogenesis of SSc-DUs is incompletely understood, a key

* Corresponding author.
E-mail address: Michael.hughes-6@postgrad.manchester.ac.uk (M. Hughes).

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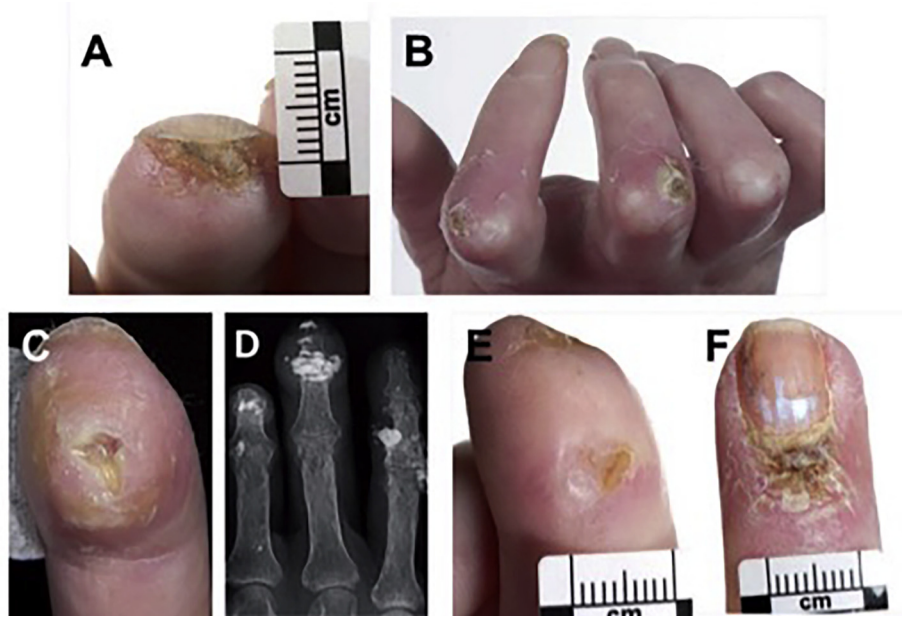

Fig. 1. DUs in SSc. A: Fingertip DU. B: Extensor DUs. C&D: DU overlying subcutaneous calcinosis (C) as seen on a plain radiograph (D) of the hand. E&F: DUs occurring on the lateral aspect (E) and the nailbed of the fingers (F). Figure reproduced with permission from Oxford University Press [7].

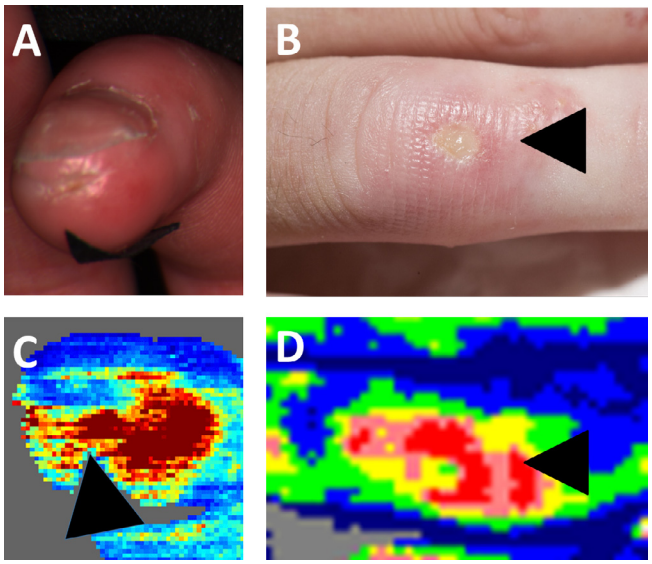

Fig. 2. Imaging DUs in SSc. Images A & B are clinical images of a fingertip (A) and extensor (B) DU. Corresponding laser Doppler images are presented in C & D, respectively, depicting reduced perfusion to the centre of both types of DU compared to the surrounding tissue. In all the images, the position of the DU is indicated by a black triangle.

issue operationally is that recent clinical trials of drug therapies for SSc-associated vasculopathy [13,14,18,19] have specifically excluded extensor aspect DUs, presumably on the basis that these are not considered 'ischaemic' in aetiology, and therefore not likely to benefit from vasoactive drug therapies.

Hypothesis.

Our hypothesis is that is that DUs occurring at sites other than the fingertips, in particular, those overlying the extensor aspect of the hands, may also have a potentially reversible ischaemic component. If so, then this would strongly warrant inclusion of these common, and to date, neglected DU types in the design of future clinical trials of SSc-related digital vasculopathy.

Evidence for an ischemic aetiology to SSc-DUs

The emerging evidence base to support an ischaemic drive to SSc-DUs shall now be discussed under the following headings: 'microvascular imaging', 'structural microvascular' and 'functional microvascular disease', 'macrovascular involvement' and 'vascular associates'. It is important to highlight that these headings are arbitrary, and also intrinsically interlinked. Another important point is that many 'DU associations' have been examined for either 'any' (including extensor) DUs or solely fingertip DUs. Therefore, it is not always possible when reviewing previous research studies to separate out the associations between the degree of SSc-related vascular disease and the individual subtypes of DUs. When reviewing the previous studies, where possible, we will describe which type(s) of DUs are being discussed.

Microvascular imaging

Both fingertip and extensor DUs have been shown by objective microvascular (laser Doppler and speckle) imaging to be relatively ischaemic compared to surrounding non-ulcerated skin [20,21], with a reduction in ischaemia observed with DU healing [20,21]. Mechanical factors such as skin stretching over extensor surfaces may also be relevant and lead to further compromise at these sites. An example of laser Doppler imaging of both a fingertip and extensor DU depicting reduced perfusion to the centre (compared to the surrounding tissue) is provided in Fig. 2. There is often a relative hyperaemia of the skin immediately surrounding the ischaemic DU centre [21,22], the aetiology of which at present is unclear, and this could be important in DU healing. In a recent double-blind, crossover, placebo controlled study of the vasodilator glyceryl trinitrate (GTN), applied topically as ointment directly to SSc-related DUs, GTN resulted in a significant increase in perfusion to the ischaemic centre (and also to a lesser extent to the surrounding tissue), with a similar response observed with both fingertip and extensor aspect DUs [22].

Structural microvascular disease

Nailfold capillary abnormalities have been reported by several