excretion of urate during the reduction in systemic inflammation and the potential mechanism.

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P.R. conceived the study. All authors designed the study. D.P. and P.R. collected the data. All authors wrote the manuscript and approved the final version for publication.

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A pilot study of cutaneous oxygenation and perfusion in systemic sclerosis-related digital calcinosis

Sir, Up to a quarter of patients with SSc will develop s.c. calcinotic deposits, which are often painful and can perforate the skin, causing ulceration [1–3]. The underlying aetiology is unknown and there is currently no effective treatment. Our previous study assessing plain radiographs for the presence of acro-osteolysis and calcinosis suggested a link between severe digital ischaemia (assessed by previous in-patient intravenous prostanooid therapy, surgical debridement or amputation of the digits), acro-osteolysis and calcinosis [4]. Others have also suggested that ischaemia may contribute to calcinosi

devolution [2, 5]. The aim of this study was to elucidate the pathophysiology of SSc-related calcinosis using non-invasive imaging modalities that allow the measurement of oxygenation and blood flow (perfusion) around sites of calcinosis. Specifically, the study tested the hypotheses that hypoxia and ischaemia ‘drive’ the development of calcium deposition; the severity of oxygenation and perfusion changes are related to the size and depth of the calcinosis.

Twenty-one patients with SSc-related calcinosis of the hands participated in the study. All were female, with a median age of 63 years [interquartile range (IQR) 55–70], disease duration since onset of first non-RP feature 14 years (IQR 9–23), RP duration 23 years (IQR 12–36), 18 with lcSSc, 3 with dcSSc and 16 ACA positive. Images were obtained at the site of the calcinosis and at an adjacent site of unaffected skin (Fig. 1). Measurements of oxygenation were extracted from images taken by a bespoke multispectral imager and broadband light source, taking several images over multiple wavelengths in order to calculate oxygenation based on deoxyhaemoglobin and oxyhaemoglobin absorption spectra (as described previously [6]). Perfusion was measured from images taken by three imaging techniques: thermography, a pseudo-measure of perfusion (FLIR ONE, FLIR Systems, Täby, Sweden) that images the vasculature of the skin and perfusion changes are related to the size and depth of the calcinosis.

Images were obtained at the site of the calcinosis and at an adjacent site of unaffected skin (Fig. 1). Measurements of oxygenation were extracted from images taken by a bespoke multispectral imager and broadband light source, taking several images over multiple wavelengths in order to calculate oxygenation based on deoxyhaemoglobin and oxyhaemoglobin absorption spectra (as described previously [6]). Perfusion was measured from images taken by three imaging techniques: thermography, a pseudo-measure of perfusion (FLIR ONE, FLIR Systems, Täby, Sweden) that images the vasculature of the skin and upper layers of the underlying superficial muscle; laser Doppler imaging (MOORLDI2, Moor Instruments, Devon, UK), which measures superficial and deeper cutaneous microvascular levels; and laser speckle contrast imaging (MOORFLPI2, Moor Instruments), which images the upper levels of the cutaneous microcirculation. Lesion area and depth were assessed by high-resolution US images in order to determine the size and depth of the lesion (US imaging of calcinosis has been previously reported as a
possible alternative to plain radiography for demonstrating/calculating calcinosis [7, 8].

Wilcoxon signed rank tests were performed to examine whether there was a significant difference between measurements obtained at the site of calcinosis and the adjacent skin site. Spearman’s ρ correlations were performed to examine the relationships between measurements. The study complied with the Declaration of Helsinki and was approved by the North-West Research Ethics Committee 6. All participants gave written consent.

Twenty-one lesions were imaged, one calcinotic lesion from each patient (example shown in Fig. 1). One patient did not undergo laser speckle contrast imaging due to technical reasons. Two patients did not have US images due to having open wounds. Due to the availability of equipment, only 14 lesions were imaged for oxygenation.

There was no difference in the oxygenation at the site of calcinosis vs the adjacent site (n = 14): median 0.15 [interquartile range (IQR) 0.07–0.22] vs 0.16 (0.00–0.21) arbitrary units, respectively, P = 0.38. Skin temperature as imaged by thermal camera was similar between all calcinosis and adjacent sites (n = 21): 31.4°C (IQR 28.4–35.6) vs 32.8 (28.4–35.7), P = 0.052. Perfusion as measured by laser Doppler imaging was lower in 13 of 21 calcinosis sites as compared with the adjacent site, but grouped comparison of perfusion was not significantly decreased [349.0 (IQR 111.05–757.7) vs 390.9 (156.3–653.0), P = 0.64]. However, perfusion as measured by laser speckle contrast imaging was reduced at 19 of 20 calcinosis sites as compared with adjacent sites [121.6 (IQR 55.7–226.4) vs 265.4 (89.6–446.9) arbitrary perfusion units, P < 0.01] (Fig. 1 shows images, arrows indicating calcinosis, blue representing relatively low perfusion/temperature). The median depth of the calcinoses was 1.5 mm (IQR 1.11–2.07) and the median lesion cross-sectional area was 3.06 mm² (IQR 2.33–4.62). There were no relationships (Spearman rank correlations were non-significant) between the size and depth of the calcinosis and oxygenation or perfusion.

In conclusion, laser speckle contrast imaging, which images superficial skin layers, demonstrated significant differences in perfusion between calcinotic and adjacent area perfusion and so our findings provide further support for an ischaemic contribution to calcinosis formation. Laser Doppler imaging and thermography that imaged deeper layers of the skin and s.c. tissue showed a trend towards decreased skin perfusion, but indicated that deeper layers of the skin are potentially less affected (than superficial layers) by ischaemia at calcinotic sites. That perfusion was decreased in the area of the calcinosis vs the adjacent skin may be due to pressure effects on the skin leading to ischaemia (calcinosis typically occurs at pressure points), or it may be that calcinosis develops in areas that are underperfused for other reasons.

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Fig. 1 Photograph/perfusion imaging of digital calcinosis alongside boxplot of perfusion at the site of calcinosis and an adjacent unaffected site.
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Evaluating patient-reported fatigue and serum biomarkers in axial spondyloarthritis

Rheumatology key message

- Fatigued AS patients demonstrate higher MIP1β and VEGF, but patients on TNFi have lower MIP1β.

Dear Editor, fatigue is a common symptom in patients with axial spondyloarthritis (axSpA), having been described by 67.2% of patients with AS, and a similar rate in non-radiographic axial spondyloarthritis (nr-axSpA, 68.2%) [1].

Fatigue impacts upon quality of life [2], work productivity [3] and is associated with anxiety and depression [4].

We evaluated a broad selection of serum biomarkers (Supplementary Fig. S1, available at Rheumatology online), in a large cross-sectional mixed cohort of axSpA patients. The objective was to identify biomarker signals related to patient reported fatigue, defined by responses to Question 1 of the BASDAI [5], and explore the relationship with disease activity.

Fatigued AS patients demonstrate higher MIP1β and VEGF, but patients on TNFi have lower MIP1β.

The Bath Spondyloarthritis Biobank (Research Ethics Council reference 13/SW/0096) at the Royal National Hospital for Rheumatic Diseases (Bath) is a longitudinal database of patients over the age of 18 years, being referred with a suspected or confirmed diagnosis of axSpA, following written patient consent. At the time of this study, the Biobank comprised 1176 patients with confirmed diagnoses, 77% with AS. The study was conducted in line with the principles of the declaration of Helsinki.

Demographic and clinical information, patient-reported outcome measures (BASDAI, BASFI, patient global and pain visual analogue scales) and BASMI are collected during routine clinical visits. Questionnaire and metrology data completed closest to the date of biobank enrolment was used for analysis.

Patients included in the study were drawn from the database based upon the completeness of their data (clinical data and serology) and had a confirmed diagnosis of AS (modified New York criteria), nr-axSpA [Assessment of SpondyloArthritis international Society (ASAS) criteria] or mechanical back pain (MBP). A single 50 ml blood sample (serum and DNA) was collected at the time of enrolment into the Biobank, and all samples were analysed centrally by Myriad RBM (Austin, TX, USA) using the 47-protein Lumina Panel (Human Inflammation Multi Analyte Profile v 1.0 multiplex and Ultra-High Sensitive MCP-1 ELISA assays).

For each biomarker, lowest limit of quantitation (LLOQ), lowest amount of an analyte quantitatively determined with acceptable precision, where the coefficient of variation after serial dilutions is 30%) and serum low to high range (based upon 95% of the sample results from 100 healthy individuals) were reported.

Descriptive statistics were applied, using IBM SPSS Statistics version 24.0. All data were tested for normality using the Shapiro–Wilks test and QQ plots. Where biomarker results were below the LLOQ, these were recoded as 0. Data were described using means (s.d.) or median (interquartile range) as suitable. Where appropriate, Pearson Chi-squared, Mann–Whitney U or Kruskal–Wallis tests were employed to evaluate distributions between independent samples, and Spearman rank correlation coefficients were used to assess associations between non-parametric continuous independent samples.

Characteristics of the 273 patients are shown in Table 1: 195 (71.4%) were AS, 27 (9.9%) nr-axSpA and 51 (18.6%) MBP. A total of 88.8% of the AS cohort were Human leucocyte antigen (HLA) B27 positive, compared with 77.8% in the nr-axSpA cohort and only 13.7% of MBP. AS patients were older (mean age 53.8 years, vs 34.0 and 29.9 years in the nr-axSpA and MBP, P < 0.01), and had a higher proportion of males (74.4%, vs 44.4 and 43.1%, respectively, P < 0.01). Fifty-eight (29.7%) AS patients and only one nr-axSpA were currently on anti-TNF medications. Mean (s.d.) disease duration for AS was 22.5 years (13.6) and 1.8 years (4.2) in non-radiographic patients (P < 0.01).