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Letter to the Editor (other)

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Abnormalities of selenium but not of copper homeostasis may drive tissue fibrosis in patients with systemic sclerosis**Rheumatology key message**

- Abnormalities of selenium but not of copper homeostasis may contribute to tissue fibrosis in SSc.

SIR, SSc is a complex autoimmune CTD characterized by fibrosis of the skin and internal organs, vascular abnormalities and immune system activation [1]. Although there have been significant advancements in identifying the cellular and molecular abnormalities that contribute to the disease process, the pathogenesis of SSc remains unknown. In recent years, abnormalities in copper homeostasis have been implicated in the pathogenesis of diabetes mellitus [2, 3] and other diseases, including (but not limited to) Alzheimer's disease and heart failure [3]. Selective copper chelation is an exciting potential therapeutic intervention for diabetes (and other implicated diseases), with encouraging results to date in non-clinical models [3], including amelioration of tissue fibrosis [4]. Raised ceruloplasmin levels have previously been reported in patients with SSc [5]. Both SSc and diabetes share many common pathogenic features (including oxidative stress and increased glycation end products). Therefore the aim of our study was to test the hypothesis that copper homeostasis is aberrant in patients with SSc, because if so, then copper chelation

could be a possible novel therapeutic approach. Specific objectives were to compare 24 h urinary copper excretion and circulating levels of copper, ceruloplasmin, zinc, selenium, albumin, HbA1c and CRP in patients with SSc and healthy controls.

Twenty patients with SSc and 20 age- and sex-matched healthy controls were recruited into the study. Exclusion criteria included conditions (e.g. diabetes and Wilson's disease) and drug treatment (e.g. penicillamine) that are known to affect copper homeostasis. No patients included in the study were receiving parenteral nutrition. Patients were recruited to include both SSc subtypes (lcSSc and dcSSc) and patients with early and late disease (defined as <5 and >5 years since the onset of the first non-RP manifestation, respectively).

Participants were provided with a 24 h urine collection container, and upon returning the 24 h urine samples, fasting blood samples were collected. Urinary copper (the minimum detectable level of the assay was 0.1 µmol/l) and serum selenium were measured by flameless atomic absorptiometry. Serum copper and zinc were measured by atomic absorption spectrophotometry, HbA1c was measured on EDTA anticoagulated whole blood by HPLC and all other routine biochemical analyses were performed using standard methods. The Haydock National Research Ethics Service Committee approved the study and signed patient consent was obtained. A number of urinary copper measurements and CRP were below the detection limit. Accordingly, the Kaplan-Meier method was used to estimate summary statistics and Peto-Prentice tests were used to make group comparisons. Other parameters were compared using Mann-Whitney tests. One patient (with early dcSSc) and

TABLE 1 Levels of circulating biochemical markers in patients with SSc and healthy controls

Biochemical parameter	Patient	Control	P-value
Copper, µmol/l	16.4 (15.3–18.5)	16.3 (14.7–19.6)	0.901
Ceruloplasmin, g/l	0.19 (0.18–0.24)	0.19 (0.16–0.21)	0.352
Zinc, µmol/l	11.6 (11.0–12.8)	13.1 (11.6–13.8)	0.085
Selenium, µmol/l	0.84 (0.80–0.95)	1.05 (0.95–1.10)	<0.001
HbA1c, mmol/mol	37.0 (36.0–40.0)	36.5 (34.0–39.0)	0.365
Sodium, mmol/l	141 (139.5–143.0)	141 (140.0–142.0)	0.636
Potassium, mmol/l	4.2 (4.1–4.5)	4.4 (4.3–4.5)	0.360
Urea, mmol/l	4.7 (3.9–5.3)	4.4 (4.1–5.7)	0.849
Creatinine, µmol/l	73.0 (61.5–79.0)	70.0 (64.5–78.5)	0.988
Alanine aminotransferase, U/l	20.0 (16.0–22.5)	23.0 (16.5–28.0)	0.220
ALP, U/l	54.0 (47.5–69.5)	60.0 (50.0–75.0)	0.511
Total bilirubin, µmol/l	7.0 (6.0–10.0)	9.0 (6.0–10.5)	0.385
Total protein, g/l	67.0 (66.0–69.5)	69.0 (66.0–72.5)	0.289
Albumin, g/l	43.0 (42.0–44.5)	45.0 (43.0–46.5)	0.010

Values are median (interquartile range).

a matching healthy control were excluded from the analysis (in error; 24 h urinary copper was not processed for the patient).

Nineteen patients with SSc [10 female (9 dcSSc and 10 lcSSc; 9 early disease and 10 late disease)] were included in the final analysis. The median age for patients was 54 years [interquartile range (IQR) 49.5–59.5 (range 28–75)] and for controls was 55 years [IQR 50–60 (range 30–70)].

Urinary copper was undetectable ($<0.1 \mu\text{mol/l}$) for 13 (68%) patients and 7 (37%) controls. There was little variation in urinary copper evident in either group (range from below the detection limit to 0.3 and 0.2 in patients and controls, respectively). Median urinary copper for the patient group was $<0.1 \mu\text{mol/l}$ and for the control group was at the level of the detection limit of $0.1 \mu\text{mol/l}$ ($P=0.19$).

No difference was observed between patients and controls for serum copper, ceruloplasmin, zinc or HbA1c (Table 1). Serum albumin was lower in patients compared with controls, however, no other differences were observed in other liver or renal function tests (Table 1). CRP was undetectable in 2 (11%) patients and 6 (32%) controls, with a median CRP of 1.9 mg/l in both groups ($P=0.265$). Serum selenium was significantly lower in patients compared with controls (Table 1).

In conclusion, our data do not support the hypothesis that copper homeostasis is dysregulated in patients with SSc. Although serum albumin was lower in patients than controls, possibly reflecting the high prevalence of gastrointestinal disease in patients with SSc and the chronic disease process, this is unlikely to be clinically relevant given that all albumin values were within the reference range. The key finding from our study was that serum selenium was significantly reduced in patients with SSc, in keeping with previous studies [6, 7]. Selenium deficiency has been implicated (through free radical damage and tissue fibrosis) in the pathogenesis of myxoedematous cretinism [8]. Future research is warranted to examine the role of selenium deficiency in the pathogenesis of SSc and also to explore the relationships between selenium levels and disease subtype, autoantibody status and internal organ involvement (our study was not powered to explore these relationships). If reduced selenium levels are contributory to oxidative stress (implicated in the pathogenesis of SSc) and to fibrosis, then supplementation could represent a new, simple, therapeutic target for intervention.

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Michael Hughes¹, Garth J. S. Cooper^{2,3}, Jack Wilkinson⁴, Paul New⁵, John M. Guy⁶ and Ariane L. Herrick¹

¹Centre for Musculoskeletal Research, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, Manchester, ²Centre for Endocrinology and Diabetes, Institute of Human Development, Faculty of Medical and Human Sciences, University of Manchester, Manchester, ³Centre for Advanced Discovery and Experimental Therapeutics (CADET), Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, ⁴Research and Development, ⁵Rheumatology Directorate and ⁶Department of Clinical Biochemistry, Salford Royal NHS Foundation Trust, Salford, UK.

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Correspondence to: Michael Hughes, Manchester Academic Health Centre, Salford Royal NHS Foundation Trust, Stott Lane, Salford, Manchester M6 8HD, UK.

E-mail: michael.hughes-6@postgrad.manchester.ac.uk

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