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

TABLE 1

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

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 μmol/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 μmol/l and for the control group was at the level of the detection limit of 0.1 μmol/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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**References**