Fig. 1 Pathological and immunohistochemical analysis of skin biopsy from sites of calcification.

(A) Haematoxylin and eosin staining of calcified lesions surrounded by infiltrating inflammatory cells (original magnification 100×). (B–E) Immunohistochemical analysis: (B) CD68+ (original magnification 100×), (C) CD68+ (original magnification 400×), (D) CD3+ (original magnification 400×) and (E) CD20+ (original magnification 400×). The immunohistochemical analysis demonstrated that most infiltrating cells were CD68+ macrophages (B, C). CD3+ T cells were also observed (D), but CD20+ B cells were not (E).

Disclosure statement: The authors have declared no conflicts of interest.

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Accepted 10 September 2013

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Rheumatology 2014;53:767–769
doi:10.1093/rheumatology/ket347
Advance Access publication 5 November 2013

Profound hypomagnesaemia causing symptomatic hypocalcaemia—an underdiagnosed and potentially life-threatening problem in systemic sclerosis?

Sir, Gastrointestinal (GI) complications are common in patients with SSC: 40–70% have small bowel involvement,
often with bacterial overgrowth resulting in malabsorption [1]. Electrolyte imbalances, specifically hypocalcaemia and hypomagnesaemia, are not described in the literature but can have severe life-threatening consequences if not recognized and treated.

We present four patients with hypocalcaemia secondary to profound hypomagnesaemia, with the aim of heightening awareness that clinicians should have a low threshold for checking calcium and magnesium levels in patients with SSc. Key clinical details are given in Table 1, with further descriptions provided below.

Patient 1 was a 44-year-old female with dcSSc [2] and GI symptoms: weight loss, heartburn and occasional diarrhoea. Routine biochemistry testing at her outpatient appointment included serum adjusted calcium (adjCa) of 1.72 mmol/l and serum magnesium of 0.17 mmol/l. She was urgently contacted, and on specific questioning she reported pins and needles of her extremities for 2-3 weeks. She was admitted for i.v. infusions of magnesium sulphate and calcium gluconate at her local hospital.

Patient 2, a 44-year-old female, had long-standing lcSSc with SLE overlap and pulmonary fibrosis. When she attended for an i.v. cyclophosphamide infusion, her biochemistry profile was checked: serum adjCa was 1.81 mmol/l and serum magnesium was 0.20 mmol/l. She reported a tremor, limb twitching, peri-oral tingling and paraesthesiae of her hands for 2 weeks, but no recent GI symptoms (although occasional diarrhoea previously). On examination, Chovstek’s and Trousseau’s signs were positive. Infusions of i.v. magnesium and calcium were administered and levels normalized.

Patient 3, a 68-year-old female with lcSSc and small bowel bacterial overgrowth, was admitted after a routine biochemistry profile showed a low adjCa level. She was contacted and admitted to symptoms of hypocalcaemia (cramps and muscle spasms) and also reported a recent exacerbation of her pre-existing diarrhoea. Her serum adjCa was 1.53 mmol/l and serum magnesium was 0.23 mmol/l. Both rapidly normalized with i.v. calcium and magnesium.

Patient 4, a 46-year-old female with lcSSc, was admitted from the outpatient clinic with a variety of symptoms, including facial tingling and breathing difficulties. In the past she had occasional episodes of loose bowel movements with long-standing faecal soiling/incontinence. She attended for an i.v. cyclophosphamide infusion, her serum adjCa was 1.64 mmol/l and serum magnesium was 0.36 mmol/l. Both normalized with i.v. magnesium and calcium.

None of the four patients had sought medical advice for symptoms of hypocalcaemia, although this was immediately suspected in patient 4 at her outpatient attendance. In patients 1, 2 and 3, the biochemical abnormalities were discovered only after routine biochemistry tests. Magnesium and calcium i.v. repletion successfully normalized the biochemistry in all four patients with rapid resolution of symptoms. None of the patients had ECG abnormalities or a history of cardiac disease. Oral calcium and magnesium supplements were subsequently prescribed and continued long-term (one patient requires regular i.v. magnesium infusions). Serum albumin was normal at the time of hypocalcaemia. Three of four patients had normal renal function and negative breath tests at or around the time of hypocalcaemia. PTH levels were normal with no evidence of vitamin D deficiency to account for the biochemical abnormalities in the three patients tested.

We are not aware of hypocalcaemia secondary to hypomagnesaemia having previously been described in the context of SSc. We postulate a variety of possible causes. All four patients had some degree of diarrhoea (which is common in SSc and may lead to GI losses), although in only patient 3 was this a major symptom. The other common feature in our patients was the use of proton pump inhibitors (PPIs) for gastro-oesophageal reflux. There are several case reports of hypomagnesaemia and hypocalcaemia associated with the use of PPIs [3–5]. The mechanism of PPI-related hypomagnesaemia is not well understood. Cundy and Dissanayake [6] suggest that possible mechanisms include impaired intestinal absorption of magnesium (either through the direct effect of the drug or changes in intestinal pH) or genetic heterogeneity in the transporter proteins for magnesium. In our patients, it is possible that a combination of SSc-related GI complications and the use of PPIs resulted in the biochemical abnormalities.

In summary, severe hypomagnesaemia leading to hypocalcaemia is potentially life-threatening, especially in patients with multisystem disease such as SSc, which may include cardiac involvement. A major concern is that had the low magnesium and calcium levels gone unrecognized for any longer in our four patients, the clinical

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eGFR: estimated glomerular filtration rate; n/a: not available.
outcome could have been very different. In SSc, malab- 
sorption is the most likely aetiology, but other causes 
should be considered, including PPIs. We believe that 
at-risk patients with SSc (those with nutritional problems 
and/or diarrhoea) should be screened for hypomagnes-
aemia. The US Food and Drug Administration recently 
suggested regular monitoring of serum magnesium 
levels in long-term PPI use [7]. As most patients with 
SSc are on PPI therapy, there may even be a case for 
regular checks of serum magnesium and calcium.

**Rheumatology key message**

- At-risk patients with SSc (with nutritional problems 
  and/or diarrhoea) should be screened for 
hypomagnesaemia.

Disclosure statement: The authors have declared no conflicts of interest.

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Accepted 6 September 2013

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