## Vitamin D, or wait and see?

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Dear Editor,

In March 2011, a previously healthy 50-year-old woman underwent an apicotomy (#36) and extraction of two elements (#15, 47) because of progressive mandibular bone resorption and radix fractures. Orthopantomogram (figure 1A) and dental X-ray (figures 1B and C) showed radiolucent spots and loss of the lamina dura, suggesting bone resorption and/or inflammation. Histopathological examination was consistent with undermining bone resorption, showing polynuclear osteoclast-like giant cells and mononuclear fibroblast-like cells, findings associated with either a giant cell granuloma or hyperparathyroidism. As endocrine work-up revealed a parathyroid hormone (PTH) serum level of 88.4 pmol/l (reference 0.6 to 6.7 pmol/l) and a normal calcium level of 2.46 mmol/l (reference 2.20 to 2.60 mmol/l, albumin 43 g/l), the patient was referred to the Outpatient Clinic of Endocrinology. Further analysis showed low 25-hydroxy-vitamin D (25-OHD) of 23 nmol/l (reference 75 to 250 nmol/l), elevated serum creatinine compared with a measurement in 2009 (122 and 74 µmol/l, respectively), and a normal phosphate level of 0.76 mmol/l. We concluded primary hyperparathyroidism (PHP) and concomitant vitamin D deficiency, and hypothesised mandibular osteitis fibrosa cystica. In accordance with the current recommendations to initiate 25-OHD supplementation in patients with serum levels below 50 nmol/l,<sup>1</sup> we started treatment with 50,000 IU (1.25 mg) colecalciferol orally once every two weeks. Six days later, the patient had developed severe hypercalcaemia (Ca 3.83 mmol/l, albumin 45 g/l), requiring admission to the Medium Care Unit for treatment with intravenous fluid and pamidronate. Parathyroid scintigraphy with tetrofosmin (99m)Tc and ultrasound of the neck were suggestive of a parathyroid adenoma on the right side, which was surgically extirpated one week later. The postoperative course was complicated by severe and persistent hypocalcaemia for which the patient needed intravenous treatment. Pathological examination of the extirpated parathyroid gland confirmed an adenoma.

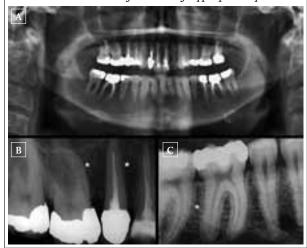
In our patient, hypercalcaemia in the context of primary hyperparathyroidism had obviously been masked by concomitant 25-OHD deficiency. The underlying mechanism of the massive calcium increase after administration of vitamin D is unclear. Although a number of vitamin D receptor polymorphisms are associated with the risk of primary hyperparathyroidism, further research is needed to elucidate their role in the calcium response to administration of vitamin D.<sup>2</sup> Vitamin D deficiency is a relatively frequent phenomenon in patients with PHP, as it has been reported to occur in 81% of patients with PHP compared with 60% in a carefully defined control group. The current guidelines, recommending 25-OHD supplementation in PHP, are based on studies reporting safe administration of 25-OHD.3-5 However, these studies did not have a randomised and controlled design and included patients with mild PHP exclusively, mean PTH values ranging from 11.9 ( $\pm$  7.5) to 16.5 ( $\pm$  9.9) pmol/l.<sup>4,5</sup> In addition to safety issues, an equally important question is whether vitamin D supplementation is beneficial. A decrease in PTH levels was seen in one prospective study,3 but not in another5 after 53 and 8 weeks of 25-OHD repletion, respectively. Of note, one study reported significantly lower serum alkaline phosphatase,3 but no differences in urinary N-telopeptide excretion or in bone mineral density.3,5 Fracture risk was not assessed. In addition to its effects on calcium and bone homeostasis, vitamin D treatment has been suggested to have beneficial effects in other (patho)physiological domains, including metabolism, immune function and atherosclerosis.<sup>6</sup> More clinical studies will be needed, however, before definitive conclusions can be drawn on the role of vitamin D in these areas.

Our case illustrates that 25-OHD repletion can induce severe hypercalcaemia in a patient with vitamin D deficiency and concomitant PHP, although this type of management is considered safe by current recommendations. The clinical benefit of 25-OHD repletion in this setting can be questioned. Until better data are available, we suggest that 25-OHD deficiency should be treated cautiously in patients with mildly elevated PTH. In patients with severe PHP and 25-OHD deficiency, the possible benefit of 25-OHD prior to parathyroidectomy does not seem to outweigh the risk of the rapid development of severe hypercalcaemia.

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Figure 1A-C. (A) Patient's orthopantomogram with periapical bone loss at the first left lower molar (#36) and severe periodontal bone loss at the right lower molar region. (B) One of the patient's dental X-rays (right upper premolars and molars) showing loss of the lamina dura (white asterisk), if compared to the dental X-ray of a normal situation (figure 1C, white asterisk). Loss of lamina dura is a manifestation of hyperparathyroidism



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