Understanding Elevated Vitamin D Measurements to Uncover Hypercalcemia Etiology

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CASE DESCRIPTION

A 69-year-old man presented to a tertiary care center with several weeks of polyuria, polydipsia, blurred vision, and confusion. His initial investigations showed an elevated serum calcium 15.4 (reference interval: 8.4 to 10.4) mg/dL (3.86 [2.10 to 2.60] mmol/L), ionized calcium 7.9 (4.6 to 5.4) mg/dL (1.97 [1.15 to 1.35] mmol/L), and phosphate 5.26 (2.17 to 4.65) mg/dL (1.70 [0.70 to 1.50] mmol/L) with a concurrent acute kidney injury, the creatinine rising from a baseline of 1.13 to 5.73 (0.57 to 1.36) mg/dL (100 to 507 [50 to 120] µmol/L). The patient had known hypertension, treated with an angiotensin receptor blocker, heterozygous hereditary hemochromatosis (C282Y/H63D) managed with phlebotomy, and had previously recovered from hepatitis virus C with therapy. He had also been using an unknown amount of 4 unregulated health supplements, with package labeling for one suggesting a vitamin D content of 1000 IU/drop (labeling was not available for the other 3).

The patient was hospitalized for 20 days, during which he was medically managed for hypercalcemia, first with intravenous fluids and empiric pamidronate, then diuretics. The initial parathyroid hormone (PTH) level was suppressed at 6 (7 to 37) pg/mL, confirming this to be non-PTH mediated hypercalcemia. Other causes such as PTH-related peptide (<2.0 [<4.2)] pmol/L), hyperthyroidism (thyroid stimulating hormone [TSH], 1.63 [0.20 to 4.00] mIU/L), myeloma (unremarkable skeletal survey and serum protein electrophoresis), and overt solid organ malignancy (based on computed tomography [CT] of the chest, abdomen, and pelvis) were excluded.

After some initial mild improvement in hypercalcemia during the first week, the serum calcium rose to >14 mg/dL (>3.5 mmol/L). The working diagnosis of vitamin D toxicity was determined based on total 25-hydroxyvitamin D (25(OH)D) of 599 (32 to 80) ng/mL (1495 [80 to 200] nmol/L) by immunoassay (DIASORIN® Liaison XL). Concomitant 1,25-dihydroxyvitamin D (1,25(OH)2D) by immunoassay (DIASORIN Liaison XL) was extremely high at 1000 (25 to 87) pg/mL (2400 [60 to 208] pmol/L) with an angiotensin-converting enzyme level of 27 (13 to 57) U/L. In the absence of imaging evidence for sarcoidosis or other granulomatous disease, the working diagnosis continued to be vitamin D intoxication. The patient's supplements were discontinued at admission, and empiric glucocorticoid treatment was administered until hospital discharge, with minimal effect upon calcium levels. Over serial observations, serum calcium slowly decreased, along with 25(OH)D and 1,25(OH)2D levels (Fig. 1).

During outpatient follow-up, 3 months later, a marked elevation in calcium and 25(OH)D once again was noted, the patient sharing that he had resumed use of his supplements. Hypervitaminosis D as the cause of hypercalcemia was queried, based on a persistently elevated 1,25(OH)2D of 510.4 (25 to 86.7) pg/mL (1225 [60 to 208] pmol/L), in addition to 25(OH)D of 351 (32 to 80) ng/mL (876 [80 to 200] nmol/L) (Fig. 1). Along with supplement discontinuation, treatment with ketoconazole was utilized for nearly 3 months during which time the calcium level normalized (1).

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A hypothesis of possible overactivation of cytochrome P450 family 27 subfamily B member 1 (*CYP27B1*, encoding for 1-α-hydroxylase) was considered, alongside disorders of vitamin D metabolism, such as a defect in the catabolic enzyme cytochrome P450 family 24 subfamily A member 1 (*CYP24A1*, encoding for 24-hydroxylase) (2), which principally makes 24,25-dihydroxyvitamin D3 (24,25(OH)2D3). By measuring 24,25(OH)2D using liquid chromatography–tandem mass spectrometry (LC-MS/MS) (Mayo Clinic Laboratories), we were able to rule out a defect in catabolism based on a normal, 25(OH)D:24,25(OH)2D, vitamin D metabolite ratio (VMR) of 19.1 (<25) (3). Simultaneously, testing via LC-MS/MS confirmed that the 25(OH)D3 was truly elevated at 359.6 ng/mL (897.5 nmol/L) (>80.1 ng/mL [>200 nmol/L], indicating toxicity possible). Repeat chest CT to follow up incidental pulmonary nodules showed a possible small granuloma; however, this was not hypermetabolic on subsequent positron emission tomography (PET). Overall, no hypermetabolic activity to suggest sarcoid was found on a full body PET/CT.

QUESTIONS TO CONSIDER	
1.	What possible etiologies should be considered when investigating non-PTH mediated hypercalcemia?
2.	What are the clinical explanations for excessive 25-hydroxyvitamin D compared to excessive 1,25-dihydroxyvitamin D?
3.	How can one explain vitamin D intoxication when the vitamin D supplement indicates a cholecalciferol content of just 1000 IU/drop?
4.	How might glucocorticoids or ketoconazole be used to treat severe hypercalcemia from various kinds of vitamin D excess disorders?
5.	What are the potential advantages of vitamin D or steroid compound measurements by LC-MS/MS compared to immunoassay?

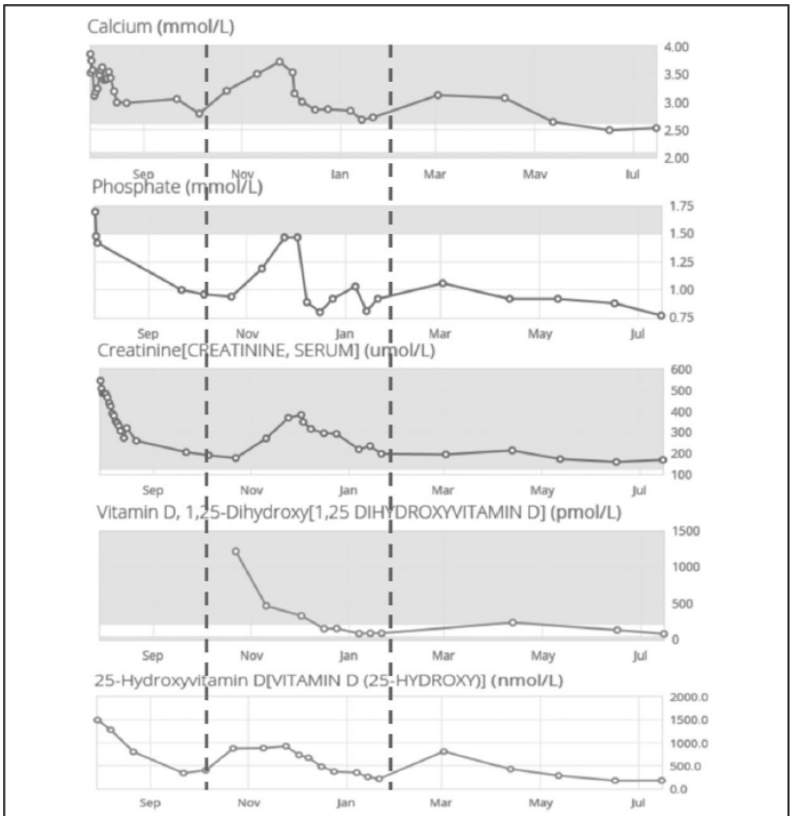

Fig. 1. Laboratory profile of a patient with non-PTH–mediated hypercalcemia ranging from initial presentation to duration of follow-up. The dashed vertical lines depict the patient's resumption of over-the-counter supplements. 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were measured via DIASORIN XL assay. Unit conversions: serum calcium mmol/L to mg/dL: ×4; serum phosphate mmol/L to mg/dL: ×3.1; creatinine μmol/L to mg/dL: ×0.01; 25-hydroxyvitamin D nmol/L to ng/mL: ×0.40; 1,25-dihydroxyvitamin D pmol/L to pg/mL: ×0.42.

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Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the June 2024 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/70/6 and follow the link to the Clinical Case Study and Commentaries.

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