

A Nontoxic Case of Vitamin D Toxicity

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ABSTRACT

Vitamin D toxicity also known as hypervitaminosis D was previously believed to be rare. But with an increase in vitamin D supplementation several cases have been reported in literature. Fat soluble vitamins like Vitamin D, due to their ability to accumulate in the body, have a higher potential for toxicity than water soluble vitamins. The main clinical consequence of vitamin D toxicity is hypercalcemia. In this report we describe an adult female patient who developed very high serum Vitamin D levels (746 ng/mL, RI: 20 to 50) as a result of medication error. In spite of such high serum concentrations the patient was without any clinical symptoms and had normal serum calcium. We critically discuss the mechanism of toxicity and hypothesize

the possible molecular/metabolic factors which might have been responsible for this nontoxic presentation. This case study highlights the fact that physicians need to consider the risk of medication errors while prescribing Vitamin D therapy. Clinical trials to study Vitamin D toxicity in humans is not possible ethically. Thus the evidence base regarding the safety profile of Vitamin D supplementation in humans has been built through case reports. This review of the paradoxical clinico-laboratory manifestation of hypervitaminosis D could possibly contribute to existing literature.

Keywords: vitamin D toxicity, hypervitaminosis D, calcium, PTH, medication error, patient safety

Vitamin D deficiency (VDD) is believed to be a global epidemic.¹ VDD has increasingly been diagnosed in patients and consequently vitamin D supplementation has been prescribed. Physicians tend to prescribe vitamin D therapy promptly; this brings up possibilities of medication errors. In particular, overdose is possible, which might lead to vitamin D toxicity (VDT).^{2,3} At Peerless Hospital, few patients with VDT have had high serum 25-hydroxy vitamin D (25OHD) levels and hypercalcemia. Herein, we discuss 1 such rare case.

Abbreviations:

VDD, vitamin D deficiency; VDT, vitamin D toxicity; 25OHD, 25-hydroxy vitamin D; RI, Reference Interval; LC-MS/MS, liquid chromatography–tandem mass spectrometry; CTx, beta crosslaps; DEXA, dual X-ray absorptiometry; DBP, D-binding protein; VDBP, vitamin D binding protein; VDR, vitamin D receptor; VDREs, vitamin D response elements; PTH, parathyroid hormone

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Case History

A 42-year-old woman with known rheumatoid arthritis who had been clinically stabilized with methotrexate and sulphasalazine therapy provided serum specimens for follow-up estimation of her vitamin D levels. She had been previously diagnosed with VDD (25OHD, 12.5 ng/mL; RI, 20 to 50 ng/mL) and was prescribed 60,000 IU of vitamin D₃, to be taken once weekly for 6 weeks. Vitamin D levels, as measured by the Roche Cobas e411 (F. Hoffmann-La Roche Ltd., Basel, Switzerland) was 746 ng/mL (RI), 20 to 50 ng/mL). However, the levels of serum calcium (9.0 mg/dL [RI, 8.6 to 10.5 mg/dL]), magnesium (1.90 mg/dL; 1.8 to 2.6 mg/dL) and phosphate (3.5 mg/dL; 2.5 to 4.5 mg/dL) were normal. When results from repeat specimens were similar, we considered assay interference and measured vitamin D levels with 2 other chemiluminescence techniques (VITROS Vitamin D [Ortho Clinical Diagnostics Inc., Raritan, NJ], 720 ng/mL; and Abbott Architect 25OH vitamin D assay [Abbott Laboratories, Abbott Park, IL], 670 ng/mL), which yielded similar results. Plasma parathyroid hormone (PTH) levels, as measured using Roche Cobas e411, were suppressed, at 8.5 pg/mL (RI, 15 to 65 pg/mL). Other parameters such

as blood counts and renal, thyroid, and liver function test results were unremarkable. The total 25 OH vitamin D level, as measured via liquid chromatography–tandem mass spectrometry (LC-MS/MS), was 428 ng/mL; the level of 1,25 (OH)₂ vitamin D was 74 pg/mL (RI, 15 to 70 pg/mL). The level of urinary calcium within the previous 24 hours was 280 mg (RI, 100 to 250 mg/24 hours). The level of the bone-resorption marker beta crosslaps (CTX), as measured via the Roche Cobas e411 platform, was 308 pg/mL (RI: 25 to 573 pg/mL).

The clinical history and examination results for the patient were unremarkable for VDT. She did not report nausea, vomiting, weakness, fatigue, or constipation. We observed no evidence of any aortic calcification or nephrolithiasis in abdominal imaging. X-ray images of the spine and hips were also normal; we did not perform dual X-ray absorptiometry (DEXA) scanning. The patient had been consuming a normal healthy Indian diet that provided her sufficient calcium. After probing questioning of the patient and review of her medical records, it became apparent that she had misinterpreted the intended weekly dose of vitamin D₃ and had consumed 60,000 IU daily (rather than weekly) for the previous 4 months (rather than 6 weeks).

Discussion

In patients with VDT, clinical manifestations are a consequence of elevated calcium levels rather than metabolic forms of Vitamin D.⁴ Vieth⁵ has suggested that serum vitamin D levels need to be consistently greater than 150 ng/mL to produce hypercalcemia and other clinical manifestations of toxicity. However, the mystery in the clinical and laboratory results for our patient was the absence of hypercalcemia despite the marked elevation of plasma vitamin D.

Mechanisms of Vitamin D Toxicity

Jones⁶ has described 3 mechanisms for vitamin D toxicity:

1) Toxicity mediated by the active hormonal form 1,25 (OH)₂ vitamin D.

2) The entry of free 25OHD to switch on gene expression of vitamin D–dependent genes when markedly raised plasma 25OHD levels exceeds the binding capacity of the D-binding protein (DBP).

3) In hypervitaminosis D, metabolites (such as 25[OH]D₃; 24,25[OH]₂D₃; 25,26[OH]₂D₃; and 25[OH]D₃-26,23-lactone) saturate the DBP in the bloodstream. When this occurs, the free concentrations of certain metabolites, such as 1,25 (OH)₂ vitamin D and 25(OH)D₃, could increase significantly.

Why the Patient Had Normocalcemia

Our patient had an elevated serum 25OHD level and a 1,25 (OH)₂ vitamin D level just greater than the upper reference limits, which suggests that absorption of oral vitamin D and subsequent hydroxylation by hepatic and renal mechanisms to form the active hormone were intact. Pettifor and colleagues⁷ studied 11 members of a family with accidental vitamin D overdose and observed that the 1,25 (OH)₂ vitamin D levels in serum specimens from these individuals was within normal intervals in most of them despite the presence of hypercalcemia and other clinical manifestations of toxicity. Serum total vitamin D (25 OH D₂ + D₃) levels, as measured by LC-MS/MS, were lower than the levels obtained via chemiluminescence assays. This occurred possibly because of the cross-reactivity of vitamin D metabolites such as 24,25(OH)₂D₃; 25,26(OH)₂D₃; and 25(OH)D₃-26,23-lactone in the chemiluminescence assays.⁸ LC-MS/MS assays standardized only for 25(OH) D₂ and D₃ will not detect those entities in individuals with hypervitaminosis D. Sempos and colleagues,⁹ on behalf of the Vitamin D Standardization Program (VDSP), have noted that the VDSP is investigating 24–25-dihydroxycholecalciferol as a potential interfering substance in immunoassays.

Vitamin D binding protein (VDBP) plays a role in maintaining stable serum concentrations of vitamin D metabolites and modulates the rate of its bioavailability, activation, and end-organ responsiveness.¹⁰ It has been reported that genetically engineered mice in which DBP had been inactivated (DBP knockout mice) were markedly less susceptible to development of hypercalcemia induced by vitamin D overdose.¹¹ 25OHD concentrations in women who

have not undergone menopause are strongly related to DBP polymorphisms; however, whether such mutations are protective in VDT has not been established.¹² As a result, we were unable to perform DBP estimation in our patient.

1,25 (OH)₂ vitamin D maintains calcium homeostasis by promoting an increase in intestinal calcium uptake and bone resorption. However, in marked vitamin D toxicity, hypercalcemia is caused predominantly by increasing bone resorption.¹³ In our patient, serum bone resorption marker levels and X-ray images of the hips and spine were unremarkable. The final pathway for 1,25 OH₂ vitamin D and other D metabolites is via the vitamin D receptor (VDR). 1,25 (OH)₂ vitamin D binds to VDR and heterodimerizes with retinoid X receptor. This complex then associates with vitamin D response elements (VDREs) and recruits additional nuclear proteins to form a transcriptional preinitiation complex.¹⁴ It is known colloquially that deleterious mutations in the VDR gene cause 1,25 (OH)₂ vitamin D-resistant rickets, a rare monogenetic disease. Research has also established that several polymorphisms exist in the VDR gene; however, the clinical influence of these on VDR protein function is largely unknown.¹⁵ Such polymorphisms might have been responsible for the normocalcemia of our patient despite her markedly raised level of serum vitamin D.

Vitamin D 24-hydroxylase is the key regulator in preventing the development of high levels of 1,25 (OH)₂ vitamin D. Nesterova and colleagues¹⁶ described 2 cases in which 24-hydroxylase deficiency due to biallelic mutations in CYP24A1 caused elevated levels of serum 1,25 (OH)₂ vitamin D, hypercalciuria, and renal stones. 24 hydroxylase is necessary for the catabolism of 1,25 (OH)₂ vitamin D.¹⁶ Increased 24 hydroxylase as a result of CYP24A1 mutation, which prevented development of hypercalcemia, could have been possible in our patient. Whether medications such as methotrexate or sulphasalazine upregulate CYP24A1 is unknown to us.

In our patient, we discovered that PTH levels were suppressed, probably by the slightly elevated level of 1,25OHD; therefore, these levels could not have produced hypercalcemia. The cut-off regions where PTH and 1,25OHD suppression are linked are not clearly understood, to our knowledge. In 1992, Jacobus and colleagues¹⁷ reported the cases of 8 patients with hypervitaminosis D (with 25 OHD levels ranging between 170-665 ng/mL) as a result of excessive vitamin D

fortification of cow milk. Only 1 (25 OHD, 203 ng/mL) of those 8 patients had normocalcemia and increased urinary calcium levels despite elevated serum vitamin D levels, similar to our patient. However, the authors did not provide an explanation for this effect.

Follow-Up of the Patient

Because the patient has normal calcium levels, no active management was undertaken. We asked her to immediately discontinue vitamin D supplementation and to maintain adequate hydration; we also recommended a calcium-restricted diet. In hypervitaminosis D, ingested vitamin D is deposited and, consequently, slowly released into body fat.¹⁸ Hence, we advised our patient to undergo repeat testing of her serum vitamin D levels after 4 months.

Conclusions and Recommendations

Clinical trials of VDT with human volunteers are not possible for ethical reasons. Thus, the existing knowledge base of VDT has been built through case reports and animal experiments. This case study highlights that vitamin D metabolism is complex and that many aspects remain unknown. The possibilities that might have prevented hypercalcemia in this patient include elevated VDP leading to reduced bioavailable vitamin D, mutation in the VDR, and a hyperactive 24-hydroxylase. Generally, patients with severe VDT experience acute and dangerous hypercalcemia. Physicians need to consider the risk of medication errors while prescribing vitamin D supplementation. Critical alerts of vitamin D are relatively uncommon among laboratories. However, with the rise in VDT cases that Peerless Hospital has observed, its laboratory has formulated a policy of compulsory testing for serum calcium in all patients with vitamin D levels greater than 150 ng/mL. If calcium level results exceed 13 mg/dL, a critical alert is generated, with a comment on the report to discontinue vitamin D therapy or to evaluate possibility of surreptitious intake of multivitamin supplements rich in vitamin D. This case highlights the need to be vigilant for adverse effects of vitamin D supplementation and to maintain communication between laboratory and clinical personnel to prevent potentially dangerous incidents.

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