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Adult Hypervitaminosis D-A Case Series

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Abstract

Prolonged hypervitaminosis D can result in calcium deposition in the soft tissues (especially the kidneys and heart), changes in the central nervous system & in severe cases, death. Patients and clinicians considering supplementation above currently recommended levels should be made aware of the possible toxicities of treatment with vitamin D, and baseline calcium and parathyroid hormone and vitamin D levels should be ascertained. We report here 8 such cases, all presenting with nausea, vomiting, polyuria, polydipsia, weakness and the common history of administration of vitamin D for backache, osteoarthritis, osteoporosis, leg cramps or generalized weakness. Laboratory tests revealed hypercalcemia and hypervitaminosis D in all cases. Vitamin D intoxication from increase in vitamin D intake may have become frequent in recent years due to an understanding of the role of 25-hydroxy vitamin D in the pathogenesis of several diseases. The importance of this case series as a warning against overtreatment and unnecessary treatment with high dose vitamin D cannot be overemphasized, especially as a public health measure in a country where vitamin D deficiency in children manifesting with rickets is a risk.

Keywords: Hypervitaminosis D; Vitamin D, Cholecalciferol; Toxicity; Parathyroid; Hypercalcemia

Introduction

Vitamin D has been postulated to have a role not only in calcium/phosphate homeostasis but in the prevention of cancer, autoimmune conditions, cardiovascular disease, infections, and a number of other conditions. The nearly universal presence of Vitamin D receptor, the large number of tissues expressing CYP27B1 responsible for systemic or local production of the active hormone and the very large number of genes (about 3% of the mouse and human genome) under the control of 1,25 $(OH)_2D$ all point toward a broader role of the vitamin D endocrine system beyond the regulation of calcium and bone metabolism [1]. The essential question of how much vitamin D is needed for optimal bone and global health, however, remains unsolved [2].

Case Series

In the eight cases of hypercalcemia and hypervitaminosis D we came across, not all symptoms of vitamin D intoxication were present. Only the symptoms of nausea, vomiting, polyuria, polydipsia, weakness and the common history of administration of vitamin D were common to all the cases.

None of the patients complained of pre-existing hypercalcemia, prior history of renal stone disease, known hypersensitivity to vitamin D, severe renal or hepatic dysfunction or pregnancy or lactation. No patient had evidence of renal calcification on ultrasound. Renal and hepatic function was assessed by creatinine/ urea and alanine transaminase [ALT], aspartate transaminase [AST] and alkaline phosphatase [ALP]. Two cases had high urea and creatinine. Out of the eight cases, two were found to be hypothyroid, seven were anaemic and three had diabetes mellitus. Parathyroid levels were within reference range in all cases.

All of the patients had a history of vitamin D ingestion for over three months in the form of multiple parenteral injections or weekly oral sachets of vitamin D for various indications like backache, osteoarthritis, osteoporosis, leg cramps or generalized weakness. However there was a lack of monitoring of calcium, parathyroid hormone or vitamin D during the entire course of the treatment.

The patients had received high doses of vitamin D and no other cause of hypercalcemia was identified. Six were women and in higher age group mainly while two cases were in their thirties.

Serum levels of 25- hydroxy vitamin D(both D_2 and D_3) and parathormone (intact) (Table 1) were measured by the chemiluminescence immunoassay (CLIA) on Siemens ADVIA Centaur XP immunoassay analyzer. Routine biochemical tests were performed on Siemens Dimension Expand.

Commonly used preparations of vitamin D_3 were tablets 1000 units taken daily for 3-4 months, vitamin D injections 6,00,000 IU given IM bimonthly or monthly for about 3 months and vitamin D sachets 60,000 IU given once weekly for around 3 months. Another point noted was that the prescriptions were from local health care providers or over-the-counter medications. Therefore the strength of the formulations administered was more than recommended guidelines and the duration of medication was more than recommended duration.

We estimated average daily vitamin D intake as total ingested dose divided by duration of dosing and found the daily average dose to range from 8000 to 80,000 IU/day for patients on vitamin D_3 alone. Two patients who had average vitamin D intake as 1000 and 8000 IU/day were also taking calcium supplements daily for almost the same period of time, as shown in Table 1.

Discussion

Based on the IOM Committee's [3] conclusion that the prevalence of vitamin D inadequacy in North America has been overestimated urgent research and clinical priorities were identified, including reassessment of laboratory ranges for 25hydroxyvitamin D, to avoid problems of both

Parameter [ref range]	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age/sex	50 /F	65/F	64 /M	36/F	79/M	33 F	53F	62F
Form of vitamin D (D2 or D3) & dose ingested;	6,00,000 IU, D3	60,000 IU, D3	3,00,000 IU, D3	6,00,000 IU,D3	6,00,000 IU, D3	60,000 IU, D3	1000 IU, D3	60,000 IU, D3
dosing schedule (daily, weekly, monthly, 3-monthly, 6- monthly, or yearly);	Weekly injection	weekly	Weekly injection	Weekly injection	Monthly injection	Daily	daily	weekly
duration of dosing (number of months);	1.5 months	6 months	¾ month	1 ¼ month	3 months	6 months	6 months	4 months
estimated average daily vitamin D intake (total ingested dose divided by duration of dosing)	80,000 IU/ day	8,000 IU/day	42,857 IU/day	81,081 IU/ day	20,000 IU/day	60,000 IU/day	1000 IU/day	8,000 IU/day
Calcium supplement	--	--	--	---	---	---	calcitonin nasal spray daily once [2200 IU] since 1month + elemental calcium 500 mg daily since 4 months	elemental calcium 500 mg daily since 3 months, calcitonin nasal spray [2200 IU] since 1 month daily.
Calcium [8.5-10.2 mg/dl]	10.5	10.5	11.1	12.5	10.7	10.2	10.5	10.5
Phosphorus[2.5-4.5 mg/dl]	3.3	3.0	2.0	2.8	2.8	3	3.3	5.6
Magnesium [1.6-2.5 mg/dl]	1.9	2.1	1.8	1.9	2.0	1.9	2.0	2.5
Intact parathyroid hormone [15 - 75 pg/ml]	59.4	40.2	67	34.2	18.8	60	34	23.9
25 OH Vit D [30-100 ng/mL]	214.9	210.6	303	235	264	212	217.4	217.8
Urea [5-40 mg/dl]	35	31	43	24	103	41	39	41
Creatinine [0-1.3 mg/dl]	0.8	0.9	1.7	0.6	2.8	0.9	0.9	0.8
Uric acid [2.6-7.2 mg/dl]	3.1	4.9	4.1	4.1	5.3	4.2	4	3.6
Alkaline phosphatase [30-279U/L]	207	95	187	102	117	119	118	126
Hemoglobin [12-15 g/dl]	10.2	10.8	11.6	11.2	10.9	10.7	12.5	10
ESR [5-15 mm in 1st hour]	12	11	12	9	14	13	37	14
C Reactive protein [upto 6 mg/L]	6.6	4.68	1.0	1.2	3.2	6.5	<2	5
Rheumatoid factor [upto 20 IU/ml]	8.5	9.56	9.3	7.9	5.4	10	<6	11
Potassium [3.5-5.5 mmol/l]	3.9	3.1	3.6	3.4	3.5	3.5	3.5	3.6
Random plasma glucose [60-140 mg/dl]	140	143	134	107	138	88	254	156

Table 1: Biochemical findings in patients

under treatment and overtreatment. Their dietary reference intake [DRI] update process identified indicators consistently and causally linked to Vitamin D and calcium, determined the estimated Average Requirement (EAR; corresponding to the median intake needs of the population), calculated the intake level that would meet the requirements of at least 97.5% of the population [defined as the Recommended Dietary Allowance (RDA), corresponding to 2 SD above the median needs. The DRI process also specified the tolerable upper intake level (UL; the highest daily intake of the nutrient that is likely to pose no risk). When the evidence base is insufficient for development of the EAR/RDA, an adequate intake (AI) level may be estimated instead. The DRIs, developed for normal healthy persons in the North American population are provided separately for several age and gender life stage groups. In the case of ULs, the available data pertaining to adverse effects must first be examined for evidence of a benchmark intake (BI). Alternatively, either a no observed adverse effect level (NOAEL) or a lowest observed adverse effect level (LOAEL) is considered.

The recommended dietary allowance [RDA] for vitamin D intake is 400 IU/day in infants less than 1 year and 600 IU/day in children more than 1 year of age as suggested by US IOM. The RDA is 600 IU/d for ages 1–70 yr, corresponding on average to a serum 25-hydroxyvitamin D (25OHD) level of at least 50 nmol/liter (20 ng/ml), and 800 IU/d for those older than 70 yr [4].

An upper limit [UL] was set at 4000 IU/d for adults, corresponding to an average serum 25OHD level of 125 nmol/liter (50 ng/ml) [5] Hypervitaminosis D is characterized clinically by anorexia, nausea, vomiting, polyuria, polydipsia, constipation, weakness, and changes in mental status & biochemically by high serum levels of 25-hydroxyvitamin D, hypercalcemia and/or hypercalciuria [6].

Vitamin D excess is usually due to an excessive intake of the vitamin. As the C-1 hydroxylation is tightly regulated, it is more often seen as a result of accidental therapeutic overdose with hydroxylated pharmaceutical products rather than as a result of vitamin supplementation with non-hydroxylated prohormones; unless, of course, the prohormones are taken in very large doses (>50 000 U/d) [7]. It is also seen in about 10% of patients with sarcoidosis, tuberculosis and other granulomatous disorders, resulting from extra-renal conversion of 25-hydroxyvitamin D

to the active 1,25-dihydroxyvitamin D by the granulomata, a process that is not regulated by PTH. Such hypercalcemia responds to high doses of immunosuppressant glucocorticoid steroid like prednisolone. Women, the very young, and the elderly are most at risk for hypervitaminosis D from causes like taking prescribed vitamin D supplements, sun sensitivity, history of cancer, and consumption of vitamin D fortified milk [6]. The association of hypervitaminosis D with age may be connected to an age-related decrease in renal function & reduced ability to eliminate excess calcium. African Americans are particularly susceptible to vitamin D insufficiency because the darker color of their skin limits the amount of ultraviolet light that penetrates, thereby reducing the cutaneous synthesis of vitamin D [8].

Vitamin D toxicity involves increased concentrations of a vitamin D metabolite reaching the vitamin D receptor in the nucleus of target cells and causing exaggerated gene expression [9]. Three hypotheses explain how vitamin D metabolites increase:

- Vitamin D intake raises plasma 1 alpha-25$(OH)_2$D concentrations, which increase cellular 1-alpha 25$(OH)_2$D concentrations.
- Vitamin D intake raises plasma 25(OH)D to concentrations that exceed the vitamin D binding protein, binding capacity and "free 25(OH)D" enters the cell, where it has direct effects on gene expression.
- Vitamin D intake raises the concentrations of many vitamin D metabolites, especially vitamin D itself and 25(OH)D. These concentrations exceed the DBP binding capacity and cause release of "free" 1-alpha 25$(OH)_2$D, which enters target cells.

In patients with vitamin D intoxication, hypercalcemia, normal or high serum phosphorus levels, normal or low levels of alkaline phosphatase (ALP), high levels of serum 25OHD, low serum parathyroid hormone (PTH), and high urine calcium/creatinine are usually present [10].

There is a lack of consensus as to the optimal level of vitamin D and the dose that will bring an individual patient to a given level. This heterogeneity in findings is due to the use of unassayed vitamin D supplements, and methodologic limitations like the lack of standardization of the different analytic methods used to measure circulating 25(OH)D concentrations, resulting in both interassay and interlaboratory variability, and the lack of standard reference preparations and calibrating materials, make vitamin D status assessments difficult [11].

The Endocrine Society Guideline has been the source of much criticism for overstating the problem of vitamin D deficiency and advocating higher intakes than required both for prevention and correction of vitamin D deficiency [12,13]. Kennan et al. [14] described the two reports on vitamin D intake requirements, published in 2011: Institute of Medicine (IOM) report (on behalf of the USA and Canadian governments) and Endocrine Society's Clinical Practice Guideline (CPG) as conflicting and suggested that the CPG rate constant should be doubled to 5.0 nmol/l (2.0 ng/ml) per 100 IU per day, adopting a more risk-averse position. Rosen et al. [15] argue that high levels of intake for a wide range of conditions (like pregnant women, lactating women, obese, older people with history of non traumatic fractures) does not reflect an evidence-based approach and is therefore unwarranted. For virtually all population groups the authors stipulate the need to achieve serum levels of 30 ng/ml.

From our study we find that most patients diagnosed as vitamin D deficient are routinely treated for vitamin D deficiency despite the lack of typical deficiency indicators like low bone density, symptoms of osteoporosis and increased fracture risk. This is risky because too much vitamin D can raise calcium blood levels and ultimately result in abnormal heart rhythms, blood vessel damage, and kidney stones. As vitamin D preparations are available over the counter, and the concept of "vitamin D deficiency" is becoming widespread, the concern is on the rise. If we do not become vigilant now and stop the inadvertent use of vitamin D supplements, it will not be a surprise to see more and more cases of vitamin D toxicity in near future with many cases going undiagnosed and unreported. To prevent iatrogenic vitamin D toxicity; awareness should be increased among healthcare providers regarding the toxic potential of high doses of vitamin D including hypercalcemia, hypercalciuria, nephrocalcinosis, and even renal impairment.

If a patient presents with persistent vomiting and hypercalcemia particularly in the presence of normal parathyroid hormone, then a diagnosis of overdose of vitamin D should be suspected because its correction not only alleviates symptoms but can also prevent acute kidney injury. Large community based studies will help us find out how commonly vitamin D is prescribed empirically in mega vitamin doses leading to hypervitaminosis D. More research is also required to examine the effect of incremental doses of vitamin D from fortified foods and supplementation on vitamin D and calcium metabolism in infants, pregnant women, and women of reproductive age.

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