Clinical Endocrinology (2015) **83**, 327–331 doi: 10.1111/cen.12836

ORIGINAL ARTICLE

Vitamin D toxicity resulting from overzealous correction of vitamin D deficiency

Parjeet Kaur, Sunil Kumar Mishra and Ambrish Mithal

Division of Endocrinology and Diabetes, Medanta, the Medicity, Gurgaon, India

Summary

Background Vitamin D toxicity, often considered rare, can be life-threatening and associated with substantial morbidity, if not identified promptly.

Objective To describe clinical and biochemical features, risk factors and management of patients with vitamin D toxicity seen between January 2011 and January 2013.

Methodology Patients presenting with vitamin D toxicity, between January 2011 and January 2013, at single tertiary care centre in Delhi-NCR, India, were included. Evaluation included detailed clinical history and biochemical tests including serum calcium, phosphorus, creatinine, intact parathyroid hormone and 25-hydroxyvitamin D (25(OH)D).

Results Sixteen patients with vitamin D toxicity could be identified. Clinical manifestations included nausea, vomiting, altered sensorium, constipation, pancreatitis, acute kidney injury and weight loss. Median (range) age was 64·5 (42–86) years. Median (range) serum 25(OH)D level and median (range) serum total serum calcium level were 371 (175–1161) ng/ml and 13·0 (11·1–15·7) mg/dl, respectively. Overdose of vitamin D caused by prescription of mega-doses of vitamin D was the cause of vitamin D toxicity in all cases. Median (range) cumulative vitamin D dose was 3 600 000 (2 220 000–6 360 000) IU.

Conclusion Our data demonstrate an emergence of vitamin D toxicity as an increasingly common cause of symptomatic hypercalcaemia. Irrational use of vitamin D in mega-doses resulted in vitamin D toxicity in all cases. Awareness among healthcare providers regarding the toxic potential of high doses of vitamin D and cautious use of vitamin D supplements is the key to prevent this condition.

(Received 4 December 2014; returned for revision 27 January 2015; finally revised 8 May 2015; accepted 3 June 2015)

Correspondence: Ambrish Mithal, Medanta, the Medicity hospital, Sector-38, Gurgaon, Haryana, India -122001. Tel.: +91-9811019093; Fax: +91-124 4834 111; E-mail: ambrishmithal@hotmail.com

Introduction

Vitamin D is important for calcium absorption and bone health. Reports from across the world and India indicate that hypovitaminosis D is widespread in all age groups.[1,2] Increasing interest in vitamin D fuelled by pharmaceutical interests has led to a surge in vitamin D prescription in recent years. The optimum dose schedule and route of administration of vitamin D in asymptomatic vitamin D deficiency, however, remain controversial. Clear recommendations are lacking, particularly in the Indian setting. Physicians are often unable to appreciate the different approach required for asymptomatic vitamin D deficiency on one hand, and vitamin D deficiency-induced osteomalacia on the other. Overzealous correction of low vitamin D in individuals not having metabolic bone disease has led to the emergence of an increasing number of cases of vitamin D toxicity over recent years. We report a case series of 16 patients with vitamin D toxicity seen between Jan 2011 and Jan 2013 and discuss in detail clinical presentation, risk factors, management and prevention of vitamin D toxicity.

Methodology

We report a case series of 16 patients with vitamin D toxicity seen over a period of 2 years (Jan 2011–Jan 2013) from a single tertiary care centre in Delhi-NCR, India. Patients were referred to endocrinology department to reveal the cause of hypercalcaemia, and of these, patients fulfilling the criteria for vitamin D toxicity were included. Vitamin D toxicity was defined as elevated serum calcium level (>10·5 mg/dl) with 25(OH)D level >150 ng/ml. Detailed clinical histories were obtained in all patients. Laboratory evaluation included measurement of serum calcium, 25(OH)D, intact parathormone (iPTH), phosphorus, blood urea and serum creatinine. Serum intact PTH was measured using a chemiluminescent microparticle assay (Abbott architect i1000 SR) (normal laboratory range 15–68 pg/ml), and serum 25(OH)D was measured using a chemiluminescent microparticle assay (Abbott architect i1000 SR). We also searched electronic laboratory database at our centre for total number of 25 (OH)D estimations made and their results between years 2011 and 2013.

Results

Clinical presentation

Of 16 patients, seven patients were male and nine were female. Median (range) age was 64·5 (42–86) years. Table 1 summarizes the clinical and biochemical characteristics of all 16 patients.

Presenting clinical manifestations were nausea and vomiting ($n = 5$), altered sensorium ($n = 5$), constipation ($n = 4$), pancreatitis ($n = 2$), acute kidney injury ($n = 4$) and weight loss ($n = 2$).

Biochemical parameters are shown in Table 2. Median (range) serum 25-hydroxyvitamin D (25(OH)D) level and median (range) serum total serum calcium level were 371 (175–1161) ng/ml and 13·0 (11·1–15·7) mg/dl, respectively. Median intact parathormone level (iPTH) was 18·9 (5·0–198) pg/ml. All patients had suppressed or low normal iPTH except for one patient who had raised iPTH level. This was attributed to coexisting chronic kidney disease. Serum 25(OH)D level in this patient was 378 ng/ml with serum calcium 14·8 mg/dl, serum phosphorus 6·8 mg/dl and iPTH level 198 pg/ml. Serum 1,25-dihydroxyvitamin D (1,25(OH)2D) levels were available in nine patients with the median level (range) of 78·5 (49·7–154) pmol/l, normal range: 39–193 pmol/l.

Overdose of vitamin D (enteral or parenteral) was the cause of vitamin D toxicity in all cases. All of them were prescribed vitamin D by their primary care doctor for various indications: backache ($n = 5$), nonspecific body aches ($n = 6$) and fatigue ($n = 3$). Two patients were asymptomatic and received vitamin D after their routine biochemical check-ups revealed low serum 25(OH)D levels. Mode of vitamin D administration was intramuscular injections of vitamin D3 (each containing 600 000 IU) in six patients, oral sachets/capsules (each containing 60 000 IU) in four patients and combined oral and intramuscular in six patients. Details of route of vitamin D administration and cumulative dose in each case are shown in Table 1. Median (range) cumulative vitamin D dose received was 3 600 000 (2 220 000–6 360 000) IU and mean ± SD was 3 967 500 ± 1 257 592.

Table 3 shows the total number of 25(OH)D estimations made at our centre by various specialities and total number of

Table 2. Biochemical parameters of all patients (median (range))

Parameter	Median (range)
Age (years)	64·5 (42–86)
25 (OH)D (ng/ml)	371 (175–1161)
Serum calcium (mg/dl)	13·0 (11·1–15·7)
Serum phosphorus (mg/dl)	3·9 (2·0–6·8)
Serum creatinine (mg/dl)	1·2 (0·9–2·4)
Serum iPTH (pg/ml)	18·9 (5·0–198)

Table 3. Serum 25(OH)D estimations between years 2011 and 2013

Year	Number of biochemical tests	Number of 25(OH)D tests	25(OH)D > 150 ng/ml
2011	2 183 986	3874	23
2012	2 857 213	17 142	116
2013	3 351 094	25 332	144

Table 1. Clinical and biochemical characteristics of individual patients

Cases	Age (year)	Sex	Serum 25(OH)D (ng/ml)	Serum calcium (mg/dl)	Serum phosphorus (mg/dl)	Serum creatinine (mg/dl)	Serum iPTH (pg/ml)	Cumulative vitamin D dose (IU)	Route of vitamin D administration
Case 1	74	F	378	14·8	6·8	2·4	198	3 600 000	6 IM over 4 weeks
Case 2	58	M	289	15·2	3·9	1·1	23	4 020 000	6 IM over 1 week + 7 oral over 1 month
Case 3	67	M	604	15·0	4·5	1·7	5	6 360 000	10 IM + 6 oral over 1 month
Case 4	86	M	679·5	12·9	4·0	1·7	32·4	6 000 000	10 IM over 1 month
Case 5	70	M	537	12·8	3·8	0·7	–	4 200 000	7 IM over 2 months
Case 6	62	F	574·8	14·8	4·1	1·7	–	3 000 000	5 IM over 1 month
Case 7	83	F	>160	11·1	4·0	1·1	–	2 880 000	Oral (4 times a week) over 3 months
Case 8	42	F	>160	11·0	3·3	0·9	22	2 220 000	3 IM + 7 oral over 2 months
Case 9	78	M	175	11·0	3·5	0·9	11·3	3 600 000	6 IM over 6 weeks
Case 10	71	M	480	14·7	4·2	1·3	18·7	2 640 000	4 IM + 4 oral over 8 weeks
Case 11	61	M	389	13·7	3·6	1·7	17·9	3 600 000	Oral daily for 2 months
Case 12	56	F	302	13·1	4·2	1·4	17·5	4 200 000	6 IM + 10 oral over 3 months
Case 13	46	M	365	11·2	3·2	1·1	14·8	2 760 000	Oral (daily for 1 month followed by twice a week over 2 months)
Case 14	51	M	289	11·6	4	0·9	23	3 600 000	Oral daily for 2 months
Case 15	58	F	306	10·9	3·7	1·0	18·9	4 800 000	6 IM + 20 oral over 3 months
Case 16	68	M	1161	15·7	2·0	1·4	28	6 000 000	10 IM over 1 month

IM: Intramuscular vitamin D3 injections each containing 6 00 000 IU.
Oral: vitamin D3 sachets each containing 60 000 IU.

cases with 25(OH)D beyond toxic level (>150 ng/ml) between years 2011 and 2013. As these data were obtained by reviewing the electronic laboratory database, indications for testing serum 25(OH)D by various specialities cannot be commented upon.

Management and course

A total of twelve patients were hospitalized for the management of vitamin D toxicity. Management of hypercalcaemia in these patients primarily included intravenous fluids (0·9% normal saline), judicious use of loop diuretics, subcutaneous calcitonin and glucocorticoids. Glucocorticoid therapy used was intravenous hydrocortisone (100 mg 8 hourly) for 1 week or oral prednisolone (30–40 mg once daily) for 1–2 weeks. Ten patients also required bisphosphonate therapy (intravenous infusion of zoledronate 4 mg) to manage hypercalcaemia. Average length of hospital stay in these patients was 2 weeks, ranging from 1 week to 3 weeks. One patient presenting with altered sensorium died during the hospital stay from aspiration pneumonia.

Four patients were managed on outpatient basis, as they did not have gastrointestinal symptoms and were able to maintain adequate oral intake. All outpatients and all inpatients after discharge were instructed to maintain oral hydration, avoid calcium and vitamin D supplements for next 6 months and repeat serum calcium monthly for initial 3 months and then 3-monthly for another 9 months. Patients who were managed on outpatient basis were instructed additionally to check their serum calcium weekly for initial 1 month.

Three patients had recurrent hypercalcaemia requiring rehospitalization. Of these, one patient suffered fracture spine 1 month after discharge, following a fall due to abnormal behaviour secondary to hypercalcaemia. Other two patients who had pancreatitis as initial presentation of vitamin D toxicity had to be rehospitalized 3 months after discharge for symptomatic pancreatic pseudocyst for which one of them underwent cystojejunostomy.

Discussion

Too much vitamin D can be as harmful as too little. All cases in our series presented with symptomatic hypercalcaemia. Accurate clinical and drug history, along with the finding of raised 25 (OH)D level (>150 ng/ml) and suppressed iPTH, in the presence of hypercalcaemia, confirmed the diagnosis of vitamin D toxicity in all our cases. One case had elevated iPTH level which could be explained by coexisting chronic kidney disease.

Vitamin D toxicity is almost always an iatrogenic problem. There are case reports of vitamin D intoxication secondary to the use of over the counter supplements and even milk fortification.[3–7] Accidental consumption of very high doses of vitamin D has also been reported.[8] Our case series is an illustration of an overzealous attempt to correct vitamin D deficiency. All the cases were prescribed vitamin D much beyond the recommended pharmacological doses. Moreover, most of the patients were prescribed intramuscular injections of vitamin D containing very high dose (6 00 000 IU) at frequent intervals (daily to weekly). Parenteral preparation of vitamin D should be avoided unless there is evidence of malabsorption, and none of our patients had any symptom or suggestion of malabsorption. Four patients developed vitamin D toxicity with only oral intake of vitamin D, but they received very high doses, such as 60 000 IU daily or on alternate days over a period of 1–3 months.

Toxic dose of vitamin D has not been established. The IOM (Institute of Medicine) report concluded that doses below 10 000 IU/day are not usually associated with toxicity, whereas doses equal to or above 50 000 IU/day for several weeks or months are frequently associated with toxic side effects including documented hypercalcaemia.[9] Most of the reports of vitamin D toxicity have documented vitamin D intake of >40 000 IU/day.[10] Single high doses in paediatric population (stoss therapy) were associated with hypercalcaemia and probably hypervitaminosis D.[11] Hypercalcaemia and vitamin D toxicity were noted in children when they received total dose of 240 000–4 500 000 IU of vitamin D.[12] In this report, significant variability was noticed in the amount of vitamin D intake and serum 25(OH)D and found no relationship of serum 25(OH)D with calcium and clinical status. In our case series, the cumulative vitamin D dose was above 240 000 IU. Mean cumulative vitamin D dose received in our case series was, 3 967 500 IU over a mean period of 7·4 weeks (range: 4 weeks to 12 weeks), which corresponds to a mean vitamin D intake of 76592·66 IU/day This highlights that high doses may be associated with vitamin D toxicity. Vitamin D intoxication results in elevation of the plasma concentrations of various metabolites of vitamin D3: 25(OH)D3, 24,25(OH)2D3, 25,26(OH)2D3 and 25(OH)D3-26,23-lactone. Three major theories have been hypothesized to explain the mechanism of vitamin D toxicity. All involve activation of VDR by vitamin D metabolite in the nucleus of target cells with subsequent amplification of gene expression.[13] The three hypotheses are as follows: (i) increase in 'free 25(OH)D' leading to a direct effect on gene expression; (ii) increase in concentrations of vitamin D and its metabolites, which exceed the DBP-binding capacity, and free bound 1,25(OH)2D metabolite from DBP, thereby promoting its entry into target cells; and (iii) increase in plasma 1,25(OH)2D, which results in increased cellular 1,25 (OH)2D concentrations.

The clinical manifestations of vitamin D toxicity are a consequence of hypercalcaemia and include fatigue, generalized weakness, anorexia, polyuria/polydipsia and dehydration, constipation, nausea, vomiting, confusion, difficulty in concentration, irritability, drowsiness and coma. Pancreatitis is a rare manifestation of vitamin D toxicity. In our series, two patients presented with acute pancreatitis and one of them had to be readmitted with complicated pancreatic cyst requiring surgery. Four patients suffered from acute kidney injury due to dehydration secondary to hypercalcaemia. Serum creatinine normalized in all these patients with intravenous hydration.

In our experience, not all cases with high serum 25(OH)D levels (>150 ng/ml) manifest vitamin D toxicity. Twenty-one patients presented to us with serum 25(OH)D levels (>150 ng/ml) over a period of 2 years, of which sixteen patients developed vitamin D

toxicity (data shown in this paper), whereas five patients were asymptomatic. This is supported by other case reports in the literature, which have shown that patients may have levels of serum 25 (OH)D above 100 and up to 150 ng/ml without associated hypercalcaemia.[12,14] Significant variability in serum 25(OH)D and calcium following oral or intramuscular administration of vitamin D has been reported. The factors include compliance and adherence to regimen, types of vitamin D used (D2 *vs* D3), route of administration (oral *vs* parenteral), body weight and methods for vitamin D estimation. Further, genes regulating the metabolism of vitamin D, binding protein, and conditions associated with intestinal absorption may influence serum 25(OH)D or serum calcium status.[12,15] Other risk factors for vitamin D toxicity include extremes of ages, concurrent use of thiazide diuretics, parenteral use of vitamin D, impaired renal function and coexisting disorders such as sarcoidosis and tuberculosis. In our case series, 10 of 16 patients were elderly (age >60 years), one patient had coexisting chronic kidney disease, and 12 patients received parenteral vitamin D.

Vitamin D toxicity is an emergency, which, if not managed promptly, can be life-threatening. Intravenous hydration with normal saline is the mainstay of treatment of hypercalcaemia. Loop diuretics should be administered judiciously, as their use can exacerbate pre-existing dehydration. Glucocorticoids play an important role in the treatment of vitamin D toxicity. All our patients who were hospitalized received glucocorticoids. Additional measures to treat hypercalcaemia, if hydration alone does not succeed, include bisphosphonates and calcitonin. Five of our patients required bisphosphonate therapy, while all hospitalized patients needed calcitonin. Hypercalcaemia caused by parenteral vitamin D overdose can take a long time to normalize due to slow release of vitamin D from fat deposits. Therefore, the patient should be followed up regularly with monitoring of serum calcium and 25(OH)D for a period of 1 year. The patient should also be instructed to avoid intake of any calcium or vitamin D supplement.

Case reports and small case series of vitamin D intoxication from India have started to appear recently in the literature.[16–19] 'The poison is in the dose'. Recent awareness of the importance of vitamin D deficiency, coupled with a lack of understanding of rational pharmacotherapeutics, has led to an increase in inappropriate use of vitamin D and calcium supplements. Vitamin D supplements given under the garb of 'wellness and bone health' prescriptions, empirically for nonspecific body aches and pains, by several specialties, pass off unscrupulously as 'healthy and safe' in the patients. To our dismay, a low serum 25(OH)D level diagnosed in routine health screening is often treated with mega-doses of calcium and vitamin D supplements by enthusiastic physicians. This has jolted vitamin D toxicity an 'uncommon cause of hypercalcaemia' to 'not so uncommon cause of hypercalcaemia'. We anticipate this problem to get only worse as there is a skyrocketing trend in number of vitamin D estimations in past few years. Table 3 shows the total number of 25(OH)D estimations made at our centre and total number of cases with 25(OH)D beyond toxic level (>150 ng/ml) between years 2011 and 2013. A clear rising trend in number of vitamin D estimations, along with the number of cases with toxic levels of vitamin D can be seen. This is purely the result of overenthusiastic correction of low vitamin D in individuals not having metabolic bone disease. In addition, market of vitamin D supplements has multiplied 20 times over the last 5 years with number of brands of vitamin D increasing from just 4 in 2010 to 241 in 2014 (data obtained from AIOCD (All Indian Origin Chemists & Distributors Ltd.) Pharmasofttech AWACS (Airborne Warning and Control System) Pvt. Ltd).

Limitations of the study: (i) Serum calcium levels of the cases with 25(OH)D levels >150 ng/ml, searched from electronic laboratory database, were not looked into (ii) Although clinical experience and the present case series suggest that the number of cases of vitamin D toxicity has gone up in recent years, it is not possible to comment upon the community incidence of vitamin D toxicity. Additionally, data from previous decades are not available to make a meaningful comparison. Vitamin D toxicity is completely a preventable condition. Key preventive measures include the following: (i) awareness among healthcare providers regarding the toxic potential of high doses of vitamin D, (ii) cautious use of vitamin D supplements and avoidance of empirical treatment of nonspecific bony pains with mega-doses of vitamin D and (iii) avoidance of parenteral preparation of vitamin D unless there is evidence of malabsorption.

Conclusion

Our case series demonstrates the emergence of vitamin D toxicity as an increasingly common cause of symptomatic hypercalcaemia. Irrational use of vitamin D in mega-doses resulted in vitamin D toxicity in all cases with mortality in one patient. Awareness among healthcare providers regarding the toxic potential of high doses of vitamin D and cautious use of vitamin D supplements is the key to prevent this condition.

Disclosure

Nothing to declare.

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