Original Article

Vitamin D Toxicity: A Prospective Study from a Tertiary Care Centre in Kashmir Valley

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Abstract

Background: Vitamin D toxicity (VDT), a "not uncommon" cause of hypercalcemia, can be life-threatening and cause substantial morbidity, if not treated promptly. **Aims:** To describe presentation, management, and outcome in 32 patients with VDT diagnosed over 3 years. **Materials and Methods:** Patients presenting with VDT at a tertiary care centre in Srinagar Kashmir India were included. Evaluation included detailed history and biochemical tests including serum calcium, phosphate, creatinine, intact parathyroid hormone (iPTH), 25-hydroxy Vitamin D (25-OHD), and 24-hour urinary calcium. **Results:** The clinical manifestations of the 32 patients (median age 65; range 3–77 years) included gastrointestinal symptoms (constipation and vomiting), polyuria/polydipsia, altered sensorium, pancreatitis, acute kidney injury, and nephrocalcinosis. The median total serum calcium level was 13.95 (range 11.10-17.20) mg/dl and median 25-OHD level was 306 (range 105–2800) ng/ml. All patients had suppressed or low normal iPTH and hypercalciuria and 78% had azotemia. All patients had received multiple intramuscular injections of vitamin D_3. The median cumulative dose was 4,200,000 (range, 1,800,000-30,000,000) IU. The median time to resolution of hypercalcemia was 7 months (range 4–18 months). **Conclusion:** We conclude that VDT is an increasingly common cause of symptomatic hypercalcemia. VDT needs prolonged follow up as it takes months to abate its toxicity. Enhancing awareness among general practitioners regarding the toxicity resulting from high doses of vitamin D is the key to prevent VDT. We suggest that VDT be considered in patients, especially the elderly, presenting with polyuria, polydispsia, vomiting, azotemia, or encephalopathy.

Keywords: Hypercalcemia, pancreatitis, vitamin D, vitamin D toxicity

Introduction

In addition to its well-documented pivotal role in calcium homeostasis and bone mineralization, vitamin D is increasingly being recognized as having an important role in a number of other biological functions such as cell differentiation, inhibition of cell proliferation, and immunomodulation.[1] Vitamin D deficiency, defined as serum 25-hydroxy vitamin D (25-OHD) levels <20 ng/ml and insufficiency as 21–29 ng/ml, is a global health issue.[2] Recommended dietary allowance (RDA) as recommended by the Institute of Medicine and the Endocrine Society is 600 IU for the age group 1–70 years and 800 IU for individuals aged more than 70 years.[3] The tolerable upper intake level is 4000 IU/day for individuals aged 1–18 years and 10,000 for individuals aged more than 19 years.[3] Because of the increased awareness of vitamin D deficiency in recent years, the use of vitamin D supplements by the population has increased. There is also an escalation in the doses of vitamin D prescribed by physicians to treat symptoms presumably associated with vitamin D deficiency. This increased use of vitamin D supplements by the general population and the growing number of prescriptions of therapeutic doses without any monitoring may result in vitamin D toxicity (VDT). VDT is a potentially serious condition and the current knowledge related to VDT is limited to case reports, case series, and animal experiments. To the best of our knowledge there is a dearth of prospective study on VDT. This prospective study was undertaken with two objectives: (1) To describe the clinical and biochemical features of VDT; (2) To find time-taken for resolution of hypercalcemia due to VDT.

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Materials and Methods

This prospective study included 32 cases of VDT diagnosed and managed at our centre over a period of 3 years from August 2015 to August 2018. Patients were referred to our center for evaluation and management of hypercalcemia. VDT was defined as hypercalcemia (albumin adjusted serum calcium >10.5 mg/dl) and serum 25 OHD >100 ng/ml, with hypercalciuria (24-h urine calcium >4 mg/kg/day) and suppressed intact PTH (iPTH).[4]

The clinical evaluation included detailed history and examination. The history focused on the dose and route of administration of vitamin D. The biochemical evaluation included the measurement of serum total calcium, phosphate, iPTH, 25-OHD, albumin, and 24-h urinary calcium. As a routine, we measured 24-h urine calcium and creatinine and serum calcium, creatinine, and phosphate by automated techniques. Serum iPTH and 25-OHD were measured by DXI 800, Beckman Coulter Chemiluminescence random access analyzer (Brea, CA) while following the manufacturer's protocol. The reference range for iPTH levels is 12–88 pg/ml. For the 25-OHD assay the lowest detectable level is 2 ng/ml, total imprecision of <10% in all cases/across the assay range and linearity up to 208 ng/ml.

Management of hypercalcemia included saline hydration followed by loop diuretics in all patients and calcitonin, glucocorticoids, and/or zoledronic acid in some. After discharge, the patients were followed clinically and biochemically on a monthly basis. Serum calcium was measured every month till the resolution of hypercalcemia (two consecutive serum calcium values <10.5 mg/dl).

The study was approved by Institutional Ethics Committee. The data was analysed using the Statistical Package for the Social Sciences version 20 software program (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was performed to evaluate the distributions of continuous variables. The continuous variables have been described as median and range. The categorical variables have been described in terms of frequency and percentage. Correlation between variables was assessed by Pearson's correlation test. $P < 0.05$ was considered statistically significant.

Results

Clinical presentation

Of 32 patients, 13 patients were male and 19 were female. The median age of the patients was 65 years (range 3–77 years). The clinical and biochemical parameters are described in Table 1 and clinical manifestations in Table 2.

All the patients had received multiple intramuscular injections of vitamin D_3 each containing 600,000 IU. The median cumulative dose was 4,200,000 (range 1,800,000-30,000,000) IU. In the case of 29 patients, vitamin D_3 was prescribed by general practitioners while three patients took self-medication. Surprisingly, none of the patients had 25-OHD estimation prior to the prescription of vitamin D_3 and none was subjected to biochemical monitoring. The various indications for which patients had received vitamin D included non-specific aches (n = 19), knee osteoarthritis (n = 7), fatigue (n = 3) and back pain (n = 3). The median serum calcium level was 13.95 (range 11.10-17.20) mg/dl. Severe hypercalcemia (serum calcium ≥14 mg/dl) was documented in 18 patients (56.3%). All the patients had 25-OHD levels >100 ng/ml. The median 25-OHD level was 306 (range 105–2800) ng/ml. All patients had suppressed or low normal iPTH. The median PTH level was 8.1 (range 0.1–25.0) pg/ml. All patients had hypercalciuria, the median 24-h urinary calcium was 398 (range 123–932) mg. Over three quarter (78.1%) of our patients had azotemia.

Table 1: Clinical and biochemical parameters of patients

Parameter	Median (Range)
Age (years)	65 (3-77)
Cumulative Vitamin D dose (IU)	4,200,000 (1,800,000-30,000,000)
Time to resolution of hypercalcemia (months)	7 (4-18)
Serum calcium (mg/dl)	13.95 (11.10-17.20)
Serum phosphate (mg/dl)	3.81 (2.22-5.94)
Serum 25-OHD[a] (ng/ml)	306 (105-2800)
Serum iPTH[b] (pg/ml)	8.1 (0.1-25.0)
24-h Urinary calcium (mg/24 h)	398 (123-932)
Serum creatinine (mg/dl)	2.24 (0.53-5.69)

[a]25-OHD=25-hydroxy vitamin D; [b]iPTH=Intact parathyroid hormone

Table 2: Clinical manifestations of patients

Clinical manifestation	*n* (%)
Gastrointestinal symptoms	30 (93.7)
Azotemia	25 (78.1)
Polyuria, polydipsia	15 (46.8)
Encephalopathy	12 (37.5)
Nephrocalcinosis	6 (18.7)
Pancreatitis	4 (12.5)

Gastrointestinal symptoms (constipation, nausea, vomiting) were present in all but two patients. Fifteen (46.8%) patients had polyuria and polydipsia and 12 (37.5%) had altered sensorium. Four (12.5%) patients presented with pancreatitis as a presenting manifestation of VDT; three patients had acute severe pancreatitis while one had mild pancreatitis. We documented nephrocalcinosis in 6 (18.7%) patients.

Management and course

All patients were hospitalized for the management of hypercalcemia. All the patients received saline hydration with forced diuresis. In addition, 18 (56%) patients received glucocorticoids, 16 (50%) received zoledronic acid, and 9 (28%) received subcutaneous calcitonin. After discharge, patients were instructed to maintain oral hydration and were followed monthly with clinical assessment and serum calcium estimation. Two patients were readmitted after discharge. Out

of the 32 patients, 27 had complete resolution of hypercalcemia, 1 patient expired, and 4 were lost to follow-up. Median time of resolution was 7 months (range 4–18 months). We noticed a significant correlation between age and time of resolution of hypercalcemia, with greater time of resolution seen with increasing age ($r = 0.383$, $P < 0.05$).

Discussion

Excessive vitamin D can be harmful and lead to serious complications. All the patients presented with symptomatic hypercalcemia. Accurate drug history, along with the finding of raised 25-OHD level, hypercalcemia, suppressed iPTH and hypercalciuria confirmed the diagnosis of VDT in our patients. Hypercalciuria is one of the earliest biochemical abnormalities of VDT and precedes the development of hypercalcemia.[5] The increased excretion of urinary calcium is due to the suppression of PTH. When the kidneys are no longer able to handle the amount of calcium entering into the circulation from dietary calcium and bone calcium mobilization, the serum calcium begins to rise.

Vitamin D toxicity is almost always an iatrogenic problem and same has been highlighted in our study. All the patients were prescribed vitamin D for non-specific body aches and that too in doses much beyond the recommended pharmacological doses. Furthermore all the patients were prescribed intramuscular injections of vitamin D_3 containing very high dose (6,00,000 IU) at frequent intervals (daily to weekly). Toxic dose of vitamin D has not been established. The 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 hypercalcemia.[6] Most of the reports of VDT have documented vitamin D intake of >40 000 IU/day.[7] Median cumulative vitamin D dose received in our patients was 4,200,000 IU.

The clinical manifestations of VDT are a consequence of hypercalcemia and include gastrointestinal symptoms (constipation, nausea, vomiting), fatigue, anorexia, polyuria/polydipsia, dehydration, and neurological manifestations (difficulty in concentration, irritability, drowsiness and coma). The most common clinical manifestation in our patients was gastrointestinal symptoms (93.7%) followed by polyuria/polydipsia (46.8%) and neurological manifestations (37.5%). The mechanism of polyuria/polydipsia is hypercalcemia induced nephrogenic diabetes insipidus. Pancreatitis is a well-known but a rare manifestation of hypercalcemia.[8] In our study, four (12.5%) patients presented with pancreatitis and out of these, three patients had acute severe pancreatitis. The manifestations of VDT can result from the deposition of calcium phosphate crystals in soft tissues which can occur once the calcium-phosphate product is >60 (ectopic soft tissue calcification). In the kidneys it manifests as nephrocalcinosis; We documented nephrocalcinosis in 6 (18.7%) patients.

Vitamin D toxicity is an emergency which, if not managed promptly, can be life-threatening. Intravenous hydration with normal saline is the mainstay of the treatment of hypercalcemia. Loop diuretics should be administered only after adequate hydration. Glucocorticoids play an important role in the treatment of VDT. Eighteen of our patients received glucocorticoids. Additional modalities to treat VDT include bisphosphonates and calcitonin. In our study, 16 patients received zoledronic acid and 9 received calcitonin. Hypercalcemia caused by mega-doses of vitamin D can take a long time to normalize due to slow release of vitamin D from fat deposits. Based on the disappearance of radioactivity after injection of radioactively labelled vitamin D_3, the average whole body half-life of vitamin D has been found to be 62 days.[9] Therefore, patients need a regular follow up and periodic estimation of serum calcium. In 27 patients for whom the follow up was available, the median time for resolution of hypercalcemia was 7 months with a range of 4–18 months. The knowledge regarding VDT is limited to case reports and small case series and in these publications the time taken for resolution of hypercalcemia has not been reported.[10-14] We noticed a significant correlation between age and time of resolution of hypercalcemia, with greater time of resolution seen with increasing age.

Hypercalcemia in VDT results from increased concentration of vitamin D metabolites reaching the nuclear Vitamin D receptor (VDR) and causing exaggerated gene expressions. Two mechanisms are suggested:

1. Direct action of 25-OHD and other vitamin D metabolities on the l, 25-$(OH)_2D_3$ receptor.
2. Displacement of l, 25-$(OH)_2D_3$ from D-binding protein by the high 25-OHD levels. This leads to an increase in the concentration of active, free l, 25-$(OH)_2$D3 levels.[15]

There are several case reports and case series of VDT from India.[10-14] For several reasons VDT has emerged as a "not uncommon" cause of hypercalcemia. First, the growing awareness of medical fraternity and lay public regarding the skeletal and non-skeletal benefits of vitamin D has led to an increased use of vitamin D supplements. Second, the lack of understanding of rational pharmacotherapeutics on the part of general practioners has led to an increase in an inappropriate use of vitamin D. Third, self-medication with over the counter vitamin D preparations is also not uncommon as lay public percieve "vitamin" as beneficial, essential, and harmless. We anticipate this problem to get only worse in the near future as there is an increasing trend in the number of vitamin D estimations and vitamin D prescriptions.

Conclusion

We conclude that VDT is an increasingly common cause of symptomatic hypercalcemia and results from an inadvertent use of vitamin D in mega-doses. VDT can lead to life threatening complications like pancreatitis and nehrocalcinosis which can lead to long term morbidity. VDT also needs prolonged follow up as it takes months for resolution of toxicity. Enhancing

awareness among general practitioners regarding the toxicity of high doses of vitamin D and cautious use of vitamin D supplements is the key to prevent this condition. Finally, and importantly, we strongly suggest that VDT be considered in patients, especially the elderly, presenting with polyuria, polydipsia, vomiting, azotemia or encephalopathy in the emergency room.

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Conflicts of interest

There are no conflicts of interest.

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