"Excess gooD can be Dangerous". A case series of iatrogenic symptomatic hypercalcemia due to hypervitaminosis D

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Summary

Vitamin D is increasingly recognized to have several beneficial effects. Its toxicity, causing hypercalcemia, is considered as extremely rare. We report case series of 15 patients (most of them being elderly subjects) with iatrogenic symptomatic hypercalcemia in whom toxicity occurred due to empirical excessive administration of vitamin D by oral and parenteral route.

KEY WORDS: hypervitaminosis D; vitamin D toxicity; hypercalcemia; iatrogenic; elderly patients.

Introduction

Vitamin D is increasingly recognized to have beneficial effects in several inflammatory conditions and there is some evidence to suggest that it is associated with a reduced risk of various internal malignancies, aside from its classic physiologic effects on calcium metabolism and bone homeostasis (1). It is thought to be important for maintaining normal function of many non-skeletal tissues such as muscle, immune function as well as cell proliferation and differentiation. Studies have shown that it may be useful as adjunctive treatment for tuberculosis, psoriasis and multiple sclerosis. Vitamin D insufficiency may increase risk of Type 1 DM, insulin resistance, hypertension, depression (2) and asthma (3). Therefore, it is not surprising that supplementation of vitamin D has positive effects on health, including prevention of falls in elderly (4). Although no minimum daily dietary intake of vitamin D has been identified for adults exposed to ample sunlight (5), less than 2.0 µg/day (i.e. 80 units /day), dietary level is associated with its overt deficiency in adults (2). US National Academy of Science sets RDA for vitamin D at 15 µg/day (i.e. 600 units/day) and for people older than 70 years at 20µg/day (i.e. 800 units/day). This consumption should be encouraged by fortified or enriched foods, sub thermal sun exposure or oral vitamin D supplements (2). Although vitamin D toxicity is thought to be extremely rare, and an extremely rare cause of hypercalcemia (6), food and nutrition board guidelines specify 2000IU as highest vitamin D intake that healthy adults can consume daily without risking hypercalcemia (7). Vitamin D deficiency can be treated by oral administration of pharmacological dose of vitamin D 50000 IU/week for 6-8 weeks (2). Pharmacological doses may also be required for maintenance therapy in patients who are taking such medications as anticonvulsants. Intramuscular administration of pharmacological dose of vitamin D (250000 IU biannually) are recommended in patients with intestinal malabsorption of vitamin D. Even in these patients monitoring should be done by periodic estimation of 24-hour urinary calcium excretion, which should not exceed 250mg (8). For many people the word "vitamin" implies something that is beneficial, essential and not potentially poisonous (9). Vitamin D is toxic in large doses (10) and sporadic reports of vitamin D toxicity exist in literature (11). We report a case series of fifteen patients with symptomatic hypercalcemia in whom toxicity occurred due to excessive administration of vitamin D by oral and parenteral route.

Material and methods

In the present study we report a case series of 15 patients, nine women and six men (Figure 1), aged between 42-85 years (Figure 2) (median age 76 years with a standard deviation (SD) of 13.69 years) who presented to the Department of Medicine, Acharya Shri Chander College of Medical Sciences and Hospital, Jammu, Jammu and Kashmir between December 2009 and September 2011. All patients were residents of Jammu and Kashmir.
All the 15 patients had symptoms attributable to hypercalcemia with elevated serum calcium and serum 25-hydroxy vitamin D_3 levels. To find out the cause of hypervitaminosis D in these patients, we interviewed them (after their recovery from the confusional state) and/or their accompanying persons, in the language they could best communicate in (Kashmiri, *Dogri*, Hindi), putting special emphasis on their dietary habits, including the consumption of fortified foods. We reviewed their available previous prescriptions and medical records, inspected their medication boxes for noting the composition of medications mentioned on the labels. We reviewed medical records of the patients to find out the information regarding serum levels of calcium, phosphorus, urea, creatinine, albumin, parathormone (intact) and 25- hydroxy Vitamin D_3. Serum levels of 25- hydroxy vitamin D_3 and parathormone (intact) were measured by the electrochemiluminescence immunoassay (ECLIA) on cobase-e411 immunoassay analyzer.

Results (Table 1)

All the 15 patients were suffering form hypervitaminosis D. The most frequently noted clinical manifestations in these patients were altered sensorium (82.4%), dehydration (88.2%), vomiting (35.3%), anorexia (70.6%), fatigue (82.4%), generalized body weakness (88.2%), constipation (52.9%), polyuria (76.5%), and polydipsia (70.6%).Their average stay in the hospital was 16.47 days, ranging from 11 days to 20 days. None of the patients died du-

Table 1 - Laboratory Data on the fifteen patients with Hypervitaminosis D caused by parenteral administration of high doses of Vitamin D.

S.no	Age (years)	Sex	S.Vitamin D_3 (ng/ml)	S.cal (mg/dl)	S.phos (mg/dL)	S. PTH (pg/mL)	S.Crea (mg/dL)	No. of Vit D_3 Injections	Duration over which Vit-D received
1	76	F	158.64	12.9	3.2	5.6	1.3	8-9	1 year
2	78	F	115.56	12.59	3.0	2.5	3.5	7-8	7 months
3	60	F	118.13	13.2	3.2	6.6	3.2	Every month	1 year
4	80	F	115.2	13.7	2.8	11.15	3.4	5-7	1 year
5	84	M	112	13.4	3.6	13.2	2.1	Weekly	5 weeks
6	85	F	108.1	11.2	3.0	15.1	2.3	Every month	2 years
7	70	F	150	13	3.2	11.2	3.2	Weekly	8 weeks
8	76	F	109.2	12.8	3.26	6.65	1.4	Every month	6 months
9	82	M	114	13.1	2.9	9	1.1	8-10	1 year
10	79	F	160	10.9	4.2	8.5	1.9	7-8	10 months
11	60	M	150	15.2	3.37	7.7	1.77	Every month	2 years
12	70	M	156	13.0	3.9	4.8	2.79	30-35	2 years
13	42	M	103	11.1	2.84	6.1	1.13	5-7	1 year
14	51	F	119.6	11.0	4.0	5.2	1.4	10-12	2 years
15	50	M	164	13.52	6.1	2.6	2.4	Every month	3 years

Figure 1 - Showing sex distributions of study patients.

ring the hospital stay and during 3 months of follow-up after discharge from the hospital. Two patients were readmitted, within 1 month of discharge from the hospital, with the symptoms of altered mental status and gait instability and were found to have once again hypercalcemia and high levels of serum vitamin D_3. The median serum 25-hydroxy Vitamin D_3 level was 118.1ng/ml with SD ± 22.7ng/ml, with lowest level 103ng/ml and highest level of 164ng/ml. The median serum calcium level was 13.0mg/dl with SD ± 1.9mg/dl, with lowest level being 10.9mg/dl and highest level of 15.1mg/dl (Reference range RR: 8.5 to 10.1mg/dL). The median serum parathormone (intact) level was 6.65 pg/mL with SD ± 3.45 pg/mlL, with lowest level of 2.5 pg/ml and highest level of 15.1pg/ml (RR:14.0 to 72.0 pg/mL). Prominent associated co-morbidities in the patients were Diabetes Mellitus, Hypertension, Osteoarthritis of knees, Chronic Kidney Disease (CKD), previous stroke, urinary tract infection. All the patients were belonging to middle class and most of them were members of families belonging to literate stratum of society. None of the patients presented clinical or investigational evidence of malignancy or any granulomatous disease either during evaluation at hospital or during subsequent follow up for the next 3 months. They had no history of consumption of foods fortified with Vitamin D_3. All patients had normal CT/MRI scans of brain. Among the 15 cases, 12 had evidence of renal dysfunction with median creatinine level of 2.1mg/dl with SD ± 0.86mg/dl with lowest level 1.1 mg/dl and highest level of 3.6mg/dl. Six patients were known to have chronic kidney disease. The patients used to take vitamin D orally (in the form of tablets) and by intramuscular injections. Each ampoule for intramuscular injection contained 600,000 units of vitamin D_3 and each tablet contained 200-400 units of vitamin D plus 500-1000 milligram of elemental calcium. The injections of vitamin D_3 were prescribed empirically by qualified general practitioners. The reason given, for receiving high doses of vitamin D3, by patients or their accompanying persons, was 'to improve the general health and to reduce the frailty of elderly'.

Discussion

In all the patients of our case series, the symptomatic hypercalcemia

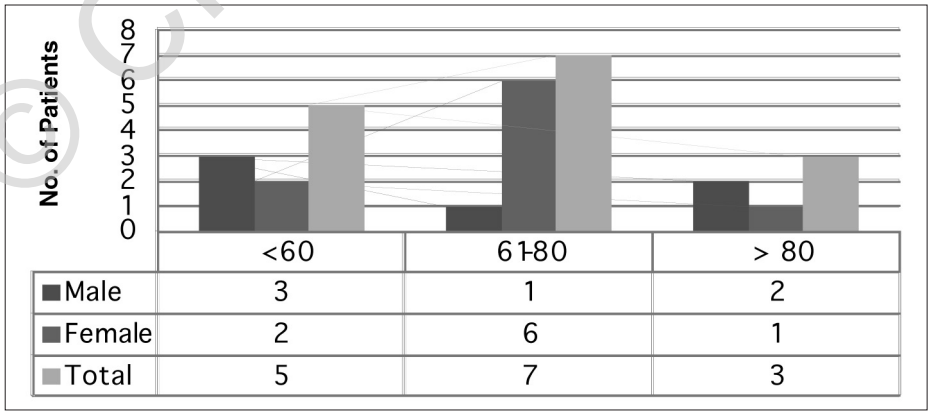

Figure 2 - Showing age distribution.

was parathyroid independent, as their serum levels of parathormone (intact) were low or low normal. The malignancy as the cause of parathormone independent hypercalcemia was largely ruled out by absence of clinical and investigational evidence of malignancy even at 3 months of follow up after discharge from the hospital. All the patients had elevated serum 25-hydroxy vitamin D_3 beyond toxic levels (>100 ng/ml). While normal serum 25 (OH) vitamin D level varies, optimal serum vitamin D level of greater 25ng/ml is sufficient for good bone health (8), and diagnosis of vitamin D intoxication is substantiated by documenting elevated levels of 25(OH) vitamin D greater than 100ng/ml (7). None of the patients had clinical or investigational evidence of granulomatous disease, which could account for their high vitamin D levels. Hypervitaminosis D has rarely been reported to occur due to excessive intake of foods commercially fortified with vitamin D e.g. fortified milk in USA (12) or due to consumption of some unusual food like bone soup (13). None of the patients was taking any unusual diet or vitamin D fortified foods. All the patients had been taking, in addition to daily oral tablets of vitamin D and calcium, mega doses of intramuscular vitamin D at frequent intervals on prescription of qualified medical practitioners. These high doses of intramuscular vitamin D were responsible for their vitamin D toxicity.

Thus, all the patients were empirically taking injectable vitamin D on prescription in doses much beyond the recommended pharmacological doses, without the laboratory evidence of vitamin D deficiency and without monitoring. Hypercalcemia due to hypervitaminosis D can be severe and prolonged, because of storage of vitamin D in the fat (13).That may be the reason why two of our patients needed readmission for symptomatic hypercalcemia. The association of symptomatic hypervitaminosis D with age may be connected to an age related decrease in the renal function and reduced ability of elderly to eliminate excess calcium (14). Presence of co- morbidities may also have predisposed these elderly patients to the toxicity of hypervitaminosis D. All the patients belonged to families of literate class of society, so they may have had access to literature highlighting the benefits of vitamin D.

We recommend that, all elderly patients who present with vague non specific symptoms like anorexia, vomiting, fatigue and altered sensorium, hypercalcemia due to hypervitaminosis D should be considered alongside the other usual causes. Large community based studies need to be done to find out how commonly vitamin D is prescribed empirically in mega vitamin doses vis-a-vis the occurrence of symptomatic or asymptomatic hypervitaminosis D. To prevent iatrogenic vitamin D toxicity awareness should be increased among healthcare providers regarding the toxic potential of mega doses of vitamin D, despite its wide margin of safety. Anything that is overdone becomes dangerous.

Conclusion

Iatrogenic vitamin D toxicity due to empirical administration of very high doses of intramuscular vitamin D injections at frequent intervals is not uncommon in the elderly patients of Jammu and Kashmir, India.

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