

High-dose Vitamin D Supplementation Precipitating Hypercalcemic Crisis in Granulomatous Disorders

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Abstract

Background: Vitamin D supplementation precipitating hypercalcemic crisis is often the first manifestation in patients with granulomatous disorders. **Methods:** We report our experience on patients presenting with hypercalcemic crisis due to granulomatous disorder and the role of Vitamin D supplementation in the precipitation of hypercalcemic crisis in them. **Results:** The study included five patients with granulomatous disorders who presented with hypercalcemic crisis. All patients initially presented with nonspecific constitutional symptoms to other health-care centers to receive high-dose Vitamin D supplementation (60,000 U/week or 600,000 U intramuscular single dose). All of these patients presented with hypercalcemic crisis (serum calcium: 16.04 ± 0.3 mg/dl) to our centers after a period of 32.8 ± 9.62 days. Three patients were diagnosed to have sarcoidosis, and two were diagnosed to have tuberculosis. All five patients had parathyroid hormone-independent hypercalcemia with elevated serum 1,25-dihydroxy Vitamin D. Serum angiotensin-converting enzyme level was elevated in all the three patients with sarcoidosis. Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography was performed in two patients with sarcoidosis which demonstrated diffusely increased tracer uptake in liver. In these two patients, liver biopsy confirmed the diagnosis. **Conclusions:** High-dose Vitamin D supplementation is most often the underlying cause of hypercalcemic crisis in patients with granulomatous disorders. Hence, high-dose Vitamin D supplementation should be used judiciously.

Keywords: Hypercalcemic crisis, sarcoidosis, Vitamin D

INTRODUCTION

The prevalence of Vitamin D deficiency is extremely high in Indian population; hence, most of them require Vitamin D supplementation.^[1] Most commonly used regimens for Vitamin D supplementation in India include high doses of oral or parenteral cholecalciferol. Intramuscular (IM) injection of cholecalciferol (6 lakh units) was the most commonly used regimen for the treatment of Vitamin D deficiency in the past whereas, in recent days, weekly oral cholecalciferol (60,000 units) for 6–8 weeks is the most commonly used regimen. Often, patients who present with nonspecific aches are supplemented with high doses of Vitamin D without evaluating for serum 25-hydroxy Vitamin D (25(OH)D) level and serum calcium levels.

Granulomatous disorders are characterized by increased activity of 1α -hydroxylase leading to increased production of 1,25-dihydroxy Vitamin D ($1,25(\text{OH})_2\text{D}$) leading to hypercalcemia.^[2–4] Small doses of Vitamin D are sufficient to cause hypercalcemic crisis in patients with granulomatous

disorders. Even increased sunlight exposure with consequent endogenous production of Vitamin D can also precipitate hypercalcemic crisis.^[5] Rarely, Vitamin D supplementation may unveil the diagnosis of granulomatous disorders by leading to hypercalcemic crisis.^[6] We report our experience with Vitamin D supplementation precipitating hypercalcemic crisis and thereby unmasking the underlying granulomatous disorder.

METHODS

The study was conducted at a tertiary health-care center. The study was approved by the Institutional Ethics Committee, and a written informed consent was obtained by all the participants. Patients with granulomatous disorders who presented with

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hypercalcemic crisis (serum calcium ≥ 14 mg/dl associated with acute symptoms or signs of hypercalcemia) over a period of 3 years (January 2012–December 2015) were included in the study.

The data regarding the symptoms, serum calcium, serum phosphorus, serum alkaline phosphatase, serum creatinine, serum albumin, serum 25(OH)D at initial presentation to other centers, recent Vitamin D supplementation dose, time interval from Vitamin D supplementation to presentation with hypercalcemic crisis, symptoms, serum calcium, serum phosphorus, serum alkaline phosphatase, serum creatinine, serum albumin, serum 25(OH)D, serum 1,25(OH)₂D, serum angiotensin converting enzyme (ACE), and serum intact parathyroid hormone (iPTH) at presentation with hypercalcemic crisis were noted. The treatment used to control hypercalcemia, temporal changes in serum calcium and serum creatinine after initiation of therapy for hypercalcemia were also noted.

Serum calcium, serum phosphorus, serum alkaline phosphatase, serum creatinine, serum albumin, and iPTH were performed by chemiluminescence method using Unicel Dx C 600 Synchron®, Beckman Coulter Ireland Inc. Before Vitamin D supplementation, serum 25(OH)D was assayed by ¹²⁵I radioimmunoassay (Diasorin, Stillwater, MN, USA); analytical sensitivity 4 ng/ml; range 5–100 ng/ml; intra- and inter-assay coefficient of variation 4.5% and 11.3%, respectively) in patient 2 and patient 5 whereas in the patient 1 and patient 3, it was assayed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). At presentation with hypercalcemic crisis, 25(OH)D was assayed by LC-MS/MS in all patients. Serum 1,25(OH)₂D and ACE were assayed by LC-MS/MS.

RESULTS

The study included five patients with granulomatous disorders who presented with hypercalcemic crisis. All patients presented

with nonspecific constitutional symptoms (generalized myalgia, malaise, anorexia, weight loss, or low-grade fever) to physicians ($n = 2$), general surgeon ($n = 1$), endocrinologist ($n = 1$), or nephrologist ($n = 1$) at other health-care centers. All subjects had normal serum calcium except one who had slightly elevated value. Severe Vitamin D deficiency was documented in all the four subjects for whom 25(OH)D values were available. All subjects received Vitamin D supplementation (60,000 U/week or 600,000 U IM single dose) [Table 1].

All of these patients presented with hypercalcemic crisis (serum calcium: 16.04 ± 0.3 mg/dl) to our centers after a period of 32.8 ± 9.62 days [Table 2]. Common symptoms at presentation with hypercalcemic crisis included nausea, vomiting, and recent weight loss [Table 3]. Hypercalcemia was associated with the elevation of serum creatinine in all patients which varied from 40% to 285% [Table 2]. All patients had PTH-independent hypercalcemia (low or low-normal parathyroid hormone levels).

Patient 1 was suspected to have malignancy associated hypercalcemia and underwent serum protein electrophoresis which was normal and ¹⁸F-fluoro-deoxy-glucose positron emission tomography/computerized tomography (¹⁸F-FDG PET/CT) which showed diffusely increased uptake in the liver along with elevated gamma glutamyl transferase (198 U/L). Then, the patient was suspected to have hepatic tuberculosis or sarcoidosis; liver biopsy was done which revealed noncaseating granulomas suggesting sarcoidosis. The patient was diagnosed to have isolated hepatic sarcoidosis. Serum ACE level and 1,25(OH)₂D were tested subsequently which were elevated [Table 3].

In patient 2, after documentation of PTH-independent hypercalcemia, serum protein electrophoresis was performed which was normal. The patient was then tested for serum ACE level and 1,25(OH)₂D which were found to be elevated.

Table 1: Characteristics of patients at initial presentation to other health-care centers (before Vitamin D supplementation)

	Sex	Age (years)	Serum calcium (mg/dl)	Serum phosphorus (mg/dl)	Serum 25(OH)D (ng/ml)	Serum ALP (U/L)	Serum creatinine (mg/dl)	Vitamin D dose received (IU)
1	Female	45	10.1	3.2	4.6	172	0.6	180,000
2	Female	42	10.7	4.9	5	118	0.54	240,000
3	Male	46	9.2	4.2	3.4	124	0.8	240,000
4	Female	38	9.6	3.6	-	143	0.7	600,000
5	Male	28	9.8	5.1	6.4	212	1	300,000

ALP: Alkaline phosphatase, 25(OH)D: 25-hydroxy Vitamin D

Table 2: Characteristics of patients at presentation to our hospital (after Vitamin D supplementation)

	Time after Vitamin D supplementation (days)	Serum 25(OH)D (ng/ml)	Serum calcium (mg/dl)	Serum phosphorus (mg/dl)	Serum ALP (U/L)	Serum iPTH (pg/ml)	Serum creatinine (mg/dl)
1	21	23.4	15.4	4.8	162	4.3	0.6
2	28	23.2	18.1	4.15	128	10.8	2.08
3	40	35.3	15.2	5.1	144	0	1.3
4	45	24.3	16.4	4.2	153	2.8	1.6
5	30	19.8	14.9	5.5	204	0	1.4

ALP: Alkaline phosphatase, iPTH: Intact parathyroid hormone, 25(OH)D: 25-hydroxy Vitamin D

Noncontrast CT chest (contrast-enhanced CT [CECT] was not performed due to elevated serum creatinine) was done to look for evidence of sarcoidosis or tuberculosis but was not contributory. Subsequently, patient underwent ^{18}F -FDG PET/CT which showed diffusely increased tracer uptake in the liver and in few mediastinal lymph nodes [Figure 1]. Liver biopsy revealed noncaseating granulomas confirming sarcoidosis.

In patient 3, after documentation of PTH-independent hypercalcemia, normal serum protein electrophoresis and elevated serum ACE level and $1,25(\text{OH})_2\text{D}$, CECT chest was performed which showed mediastinal lymphadenopathy, and then, patient was diagnosed to have sarcoidosis and transferred to the care of a rheumatologist.

Patient 4 presented with severe weight loss and vomiting. She was initially hospitalized under the care of a general surgeon with the suspicion of superior mesenteric artery

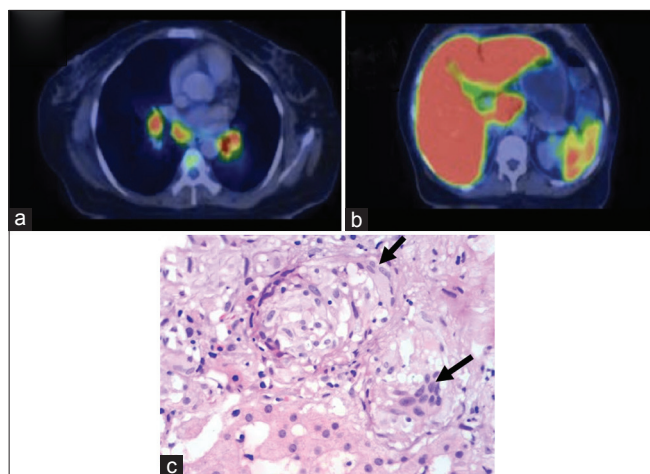


Figure 1: ^{18}F -fluoro-deoxy-glucose positron emission tomography/computerized tomography showing increased tracer uptake in mediastinal lymph nodes (a) and diffusely increased tracer uptake in liver (b). Histopathology of liver biopsy showing confluent and discrete noncaseating granulomas composed of epithelioid histiocytes, lymphocytes, and multinucleate giant cells with a few eosinophils in the background

syndrome but documentation of hypercalcemia prompted further evaluation. Erythrocyte sedimentation rate (ESR) was high (98 mm/1st h), but chest X-ray and CECT chest were not contributory. Serum protein electrophoresis was normal. Serum ACE level was normal whereas $1,25(\text{OH})_2\text{D}$ was elevated. The patient had significantly enlarged inguinal lymph nodes which were biopsied. Histopathology revealed granulomas with caseation suggestive of tuberculosis. The patient was started on antitubercular treatment (ATT). The patient responded well to ATT with improvement in appetite and weight gain.

In patient 5, who was diagnosed to have disseminated tuberculosis based on chest X-ray and liver biopsy and, was initiated on Category 1 antitubercular drugs along with parenteral cholecalciferol of 600,000 U. Patient developed vomiting after 8 days and was diagnosed to have drug-induced hepatitis (serum alanine transaminase: 218 U/L). Isoniazid, rifampicin, and pyrazinamide were stopped, and streptomycin was added. After a week, serum alanine transaminase was decreased to 38 U/L and the patient was restarted on isoniazid 5 mg/kg/day. However, vomiting persisted, and further evaluation revealed hypercalcemia. The patient had undetectable iPTH and elevated $1,25(\text{OH})_2\text{D}$.

All patients were initially treated with intravenous hydration and pamidronate (60–90 mg). There was a significant decrease in serum calcium by 24 h (1.8–3.2 mg/dl) with normalization of serum calcium over 48–120 h after pamidronate administration in all patients. Serum creatinine was also normalized in all patients over a period of 3–8 days.

DISCUSSION

In our study, Vitamin D supplementation was the precipitating factor in all patients with granulomatous disorders who presented with hypercalcemic crisis. In fact, our first patient was attributing her hypercalcemia for recent Vitamin D supplementation, but we counseled her that Vitamin D supplementation in these doses will not cause hypercalcemia, and the role of Vitamin D in precipitating hypercalcemia was

Table 3: Diagnostic tests performed to reach at the final diagnosis

	Presentation	Serum ACE (U/L)	Serum $1,25(\text{OH})_2\text{D}$ (pg/ml)	Diagnostic test	Final diagnosis
		Normal range: 8-65 (U/L)	Normal range: 20-80 (pg/ml)		
1	Vomiting Weight loss	628	128.0	^{18}F -FDG PET/CT, liver biopsy	Sarcoidosis
2	Vomiting Weight loss	207	145.76	^{18}F -FDG PET/CT, liver biopsy	Sarcoidosis
3	Vomiting Weight loss	320	113.8	CECT chest	Sarcoidosis
4	Vomiting Weight loss	20	158.3	Inguinal lymph node biopsy	Disseminated tuberculosis
5	Fever, nausea weight loss	32	133.9	Liver biopsy, chest-X-ray	Disseminated tuberculosis

ACE: Angiotensin converting enzyme, $1,25(\text{OH})_2\text{D}$: $1,25$ -dihydroxy Vitamin D, ^{18}F -FDG PET/CT: ^{18}F -Fluoro-deoxy-glucose positron emission tomography/computerized tomography, CECT: Contrast-enhanced computed tomography

not realized till the diagnosis of sarcoidosis. However, with subsequent patients presenting with hypercalcemic crisis with recent history of Vitamin D supplementation, we were sensitized to evaluate for underlying granulomatous disorder. Although in the first patient, 1,25(OH)₂D and ACE levels were tested after the diagnosis, in subsequent patients, we performed these tests before ¹⁸F-FDG PET/CT.

Hypercalcemia in sarcoidosis is reported as early as 1939.^[7] Sarcoidosis is associated with hypercalcemia in 5%–10% and hypercalciuria in 40%–60%.^[8] The role of elevated 1,25(OH)₂D in the etiology of sarcoidosis and tuberculosis-associated hypercalcemia was recognized more than four decades ago.^[9–11] It has been well-documented in the literature that increased sun exposure or low-dose Vitamin D supplementation in doses similar to recommended daily doses are sufficient enough to precipitate hypercalcemic crisis in patients with granulomatous disorders.^[12] It is not surprising that Vitamin D supplementation in higher doses is more likely to precipitate hypercalcemic crisis.^[13,14] Hence, routine supplementation with high doses of Vitamin D in patients with granulomatous disorders should be avoided.^[15]

On the other hand, Vitamin D status may be important to preserve bone health in sarcoidosis and enhance immunity in tuberculosis.^[16,17] Although the benefits of Vitamin D supplementation are not clear, recent guidelines suggest maintaining 25(OH)D level between 20 and 30 ng/ml in patients with granulomatous disorders.^[18,19] However, while doing so, close monitoring of 25(OH)D level is recommended to avoid a level more than 30 ng/ml which is associated with hypercalcemia and hypercalciuria.^[19]

The claimed benefits of Vitamin D supplementation in the promotion of health are constantly expanding. This has led to rampant increase in Vitamin D supplementation which may often precipitate hypercalcemic crisis in predisposed individuals such as hidden granulomatous disorders. Although Vitamin D supplementation cannot be discouraged owing to its ever expanding benefits, caution needs to be executed while supplementing with high doses of Vitamin D. It is highly challenging to identify patients at risk for hypercalcemic crisis. However, a high suspicion for hidden granulomatous disorders should be kept in hypovitaminosis D patients with constitutional symptoms such as weight loss, fever, and anorexia. ESR which is often done as part of general health checks along with 25(OH)D, if moderate to markedly elevated may also suggest underlying granulomatous disorder. In addition, as observed in our study slightly elevated (patient 2 and patient 5) or high normal (patient 3) serum phosphorous and/or high normal (patient 1) or slightly elevated (patient 2) serum calcium despite very low levels of serum 25(OH)D may suggest hidden granulomatous disorders.

It is often challenging to evaluate for the cause of PTH-independent hypercalcemic crisis. Often, initial evaluation is directed toward malignancy-associated hypercalcemia which is a more common cause of hypercalcemic crisis. As

we observed in our two patients with sarcoidosis, ¹⁸F-FDG PET/CT shows diffusely increased tracer uptake in the liver. Although, similar findings may be observed in patients with lymphoma or diffuse metastatic disease, hypercalcemic patients with diffusely increased tracer uptake in liver should be strongly suspected to have granulomatous disorder.^[20] In such situations, liver biopsy is a good diagnostic tool to confirm the diagnosis of underlying granulomatous disorder.

CONCLUSIONS

High-dose Vitamin D supplementation is most often the underlying cause of hypercalcemic crisis in patients with granulomatous disorders. Hence, high-dose Vitamin D supplementation should be used judiciously. The possibility of hidden granulomatous disorders should be considered in hypovitaminosis D patients who present with constitutional symptoms, elevated ESR, high or high-normal serum phosphorus, or serum calcium despite severe hypovitaminosis D.

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Conflicts of interest

There are no conflicts of interest.

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