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Original Research Article

PROFILE OF HYPERCALCEMIA WITH DEMOGRAPHIC CHARACTERISTICS, STUDY CARRIED IN A TERTIARY CARE CENTRE AT SMHS HOSPITAL, GMC, SRINAGAR.

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Abstract: Objective: The number of patients with hypercalcemia due to different causes has been ever increasing in our settings, mostly because of both prescribed as well as over the counter supplements. In order to see the trends of such patients and to understand the most common etiology, the present study was conducted in this hospital over a period of 16 months. **Methods:** Over a period of 16 months, all such patients who were admitted in this hospital with symptomatic hypercalcemia due to different causes were studied and their data was collected and interpreted. Besides serum calcium levels, the serum levels of PTH and 1, 25 dihydroxy Vitamin D were measured. **Results:** In this study of 16 months duration, a total of 24 patients were admitted with hypercalcemia, out of whom 13 patients had Vitamin D intoxication (54%) as the cause, 9 patients had malignancy, 3 patients were having primary hyperparathyroidism and 2 patients had hypercalcemia of undiagnosed cause. **Conclusion:** Hypercalcemia due to vitamin D intoxication (a treatable cause) is becoming the leading cause of hypercalcemia in this setting of a tertiary care centre.

Keywords: Elderly, hyperparathyroidism, cholecalciferol, hypercalcemia, malignancy.

Introduction: Hypercalcemia, that is, raised serum calcium level (normal range: 9 –10.5 mg/dL or 2.2–2.6 mmol/L) can be an incidental and asymptomatic laboratory finding, but since an elevated calcium level is often indicative of other diseases, a workup should be undertaken if it persists. First step in evaluating a new diagnosis of hypercalcemia is confirming it . An initial work-up should include measurement of intact parathyroid hormone, and discontinuing any medications that are likely to be causative.

Hypercalcemia can be due to excessive skeletal calcium release, increased intestinal calcium absorption, or decreased renal calcium excretion. It can be parathyroid hormone related vitamin D related, secondary to malignancy, medications, other endocrine disorders, genetic disorders or due to other causes. Primary hyperparathyroidism and malignancy account

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for the maximum (about 90%) cases of hypercalcaemia [1],[2].

Hypervitaminosis D can result from exogenous Vitamin D intake or endogenous excess production (from lymphomas, sarcoidosis, and tuberculosis). Vitamin D is a steroid hormone that is obtained through the diet or produced by the action of sunlight on its precursors in the skin. Successive hydroxylation of cholecalciferol forms active form of vitamin D, calcitriol first in the liver by 25-hydroxylation and then in the kidneys by 1-hydroxylation. Adequate vitamin D is necessary for bone formation. In the gut, it increases the absorption of calcium and phosphate. Thus, in vitamin D-mediated hypercalcemia, serum phosphate levels tend to be high. People, especially elderly, usually take dietary supplements of Vitamin D for the purpose of improving their overall health either themselves as over the counter medication without prescription or on the advice of a health practitioner [3].There has also been increasing interest by physicians in prescribing vitamin D supplements in particular for various illnesses.60 to 70% of patients fail to report the use of these supplements to their physicians [4]. Vitamin D intoxication causes hypercalcaemia by increased bone resorption[5]. Here comes the role of Inhibiting bone resorption with bisphosphonates to prevent additional calcium from being released. Serum 25OHD levels above 150 ng/ml are considered as vitamin D intoxication (VDI).

Other causes of hypercalcemia include use of thiazide diuretics in patients with an underlying mild primary hyperparathyroidism or another state of increased bone resorption, lithium therapy, immobilization, thyrotoxicosis ,milk alkali syndrome, etc. Rare causes include tertiary hyperparathyroidism in chronic kidney disease, Addisons disease, acromegaly, pheochromocytoma, familial hypocalciuric hypercalcemia, congenital lactase deficiency, use of foscarnet, etc. Some serious causes of hypercalcemia include malignancies of lung, breast, multiple myeloma, cholangiocarcinoma, etc.

Hypercalcemia in malignancy is usually mediated by PTHrP that regulates normal osteoblast (and possibly osteoclast) differentiation and activity in the bone microenvironment [6] and is responsible for normal endochondral bone formation [7],[8],[9].80% of cancer patients with hypercalcemia have PTH-rP-related hypercalcemia. Hypercalcemia is a frequent metabolic complication of multiple myeloma and carbohydrate active adrenocorticosteroid hormones are effective in reversing it [10].Clinical manifestations of multiple myeloma derive either directly from the neoplastic infiltration of bone marrow or indirectly from the aberrant functioning of humoral immunity and from secretion of clonal protein [11],[12].Bone disease in this condition is associated with excessive tumor induced, osteoclast-mediated bone destruction [13].

It is advisable to obtain serum calcium level in persons with a history of kidney stones, family history of hypercalcemia, thiazide or lithium use and in elderly patients with symptoms suggestive of hypercalcemia. Parathyroid hormone is suppressed in malignancy-associated hypercalcemia and elevated in primary hyperparathyroidism. Exclude other causes before considering parathyroid surgery in primary hyperparathyroid patients, and refer patients for the same only if certain criteria are met [14].US population-based data from Olmsted County, Minn, indicates that the prevalence of primary hyperparathyroidism is slowly decreasing [15].

Methods: In this study, a total of 24 subjects who were admitted with hypercalcemia due to different causes were included. These patients were between 44 to 80 years of age. The study was carried over a period of 16 months. Serum calcium levels were obtained at baseline and after corrective measures. The serum levels of PTH were obtained in all studied patients using the CLIA method and the corresponding suppression or increase in PTH level in the setting of hypercalcemia helped in further supporting or defying diagnosis of the cause of hypercalcemia. Serum 1,25 Dihydroxy Vitamin D were measured using CLIA method in order to diagnose coexisting or coincidental Vitamin D intoxication in these patients.

Results: In this study of 16 months duration, a total of 24 patients were admitted with hypercalcemia, out of whom 13 patients (54%) had Vitamin D intoxication as the cause, 3 patients were having primary hyperparathyroidism, 9 patients had malignancy and 2 had hypercalcemia of unknown/undiagnosed cause. Out of the total patients, 15 (62.5%) were males and 9 (37.5%) were females. The results obtained are revealed in Table 1.

Discussion: The most common cause of hypercalcemia in this tertiary care centre over the studied period was Vitamin D intoxication unlike the most common cause being primary hyperparathyroidism and malignancies as revealed by other studies [1],[2]. A parathyroid hormone/parathyroid hormone-related peptide/calcifediol assay may help differentiate among the various causes of hypercalcemia. Accelerated bone resorption by multinucleated bone resorbing osteoclasts stimulated by PTH, PTHrP and 1,25 dihydroxy vit D, have been shown to cause hypercalcemia [16].

Vitamin D intoxication is on the rise and should be included in the differential diagnosis of hypercalcemia [17],[18],[19],[20],[21],[22],[23],[24],[25]. It is a reversible condition and can be treated effectively and usually does not appear to cause long-term sequelae. Hypercalcemia resolves months before normalization of serum 25(OH) D levels. Because vitamin D is fat-soluble and 25(OH)D has a half-life of 2–3 weeks, vitamin D toxicity

usually takes weeks to months to normalize. Calcitriol is the most metabolically active form and binds to the vitamin D receptors 500 times greater than calcifediol and 1,000 times greater than cholecalciferol does[26].Inappropriate treatment or supplementation with high dose vitamin D can lead to life-threatening intoxications [27],[28],[29]. Increasing frequency of VDI may be attributable to an increase in vitamin D supplement intake due to the findings that deficiency is common and has been associated with a number of disease states [30],[31],[32]. At molecular level, 1, 25(OH) 2 D3 can increase RANKL release and decrease OPG release from osteoblastic cells and stimulate osteoclastogenesis, resulting in bone resorption. Consequently, hypercalcemia in a VDI state predominantly results from bone resorption due to the effect of vitamin D rather than through the direct participation of intestinal absorption [33].Clinical features in a patient with VDI include nausea, vomiting, abdominal pain, pancreatitis, dehydration with polyuria and polydipsia, hematuria, paraesthesias, headache, seizures, osteoporotic fractures, cardiomyopathy, bradycardia,etc. [34],[35].Treatment for vitamin D toxicity includes: discontinuing intake, a diet with low calcium and phosphorus content, intravenous hydration, loop diuretics, glucocorticoids, and calcitonin. More recently, bisphosphonates have been proven to be effective in the treatment of VDI [36],[37]. In Vitamin D mediated hypercalcemia, corticosteroids are the therapy of choice that reduce calcitriol production by macrophages and correct serum calcium within 3-5 days.

Hypercalcemic crisis is a life-threatening emergency. Aggressive intravenous rehydration is the mainstay of management in severe hypercalcemia, and antiresorptive agents, such as calcitonin and bisphosphonates, frequently can alleviate the clinical manifestations of hypercalcemic disorders. If the total serum concentration of calcium is greater than 3.50mmol/L {14.0 mg/dl}, immediate treatment is indicated regardless of symptoms [38].

In 2011, the American Medical Institute estimated tolerable upper limits of vitamin D. Administration of vitamin D has been reported to be safe at 4000 IU/day for adults and pregnant women [39]. Iatrogenic subclinical hypervitaminosis D is more commonly recorded than acute VDI. However, individual variation is important to consider with regard to VDI; vitamin D receptor polymorphisms may be associated with the development of this condition [40],[36]. Hypercalcemia is the hazard criterion for vitamin D. As per the Institute of Medicine, the tolerable upper intake level (UL) for vitamin D is 50g (2000 IU)/d. With sunlight, an adult can produce vitamin D in an amount equivalent to daily oral consumption of 250 g (10,000 IU)/d, which is a safe dose. The

additional intake of 1 g (40 IU)/day of vitamin D3 raises serum 25(OH)D by ~1 nM (0.4ng/ml). Therefore, sun-deprived adults require an intake of more than the UL for vitamin D [41]. Hypercalcemia is reported in normal adults by Narang et al. [42] above the 50g/d (2000 IU/d) UL for vitamin D intake, however, confirmatory studies using 100g (4000 IU)/d with more subjects and for longer periods have produced no detectable change in serum or urine calcium [43],[44],[45].The toxic dose of vitamin D is estimated to be greater than 100,000 IU (2,500 g) per day for a duration of at least 1 month [46].

Malignancies stand next in number and included lung carcinoma, breast carcinoma, carcinoma with unknown primary, multiple myeloma and Hodgkins lymphoma. Hypercalcemia in malignancy occurs abruptly, is severe, and portends a very poor prognosis (median survival only six weeks). For hypercalcemia of malignancy, bisphosphonates are the main treatment modality.

Limitations of the present study : Many of our patients had been bed ridden for a long time. Hypercalcemia from immobilization was first described in 1941 by Albright in a teenager with fracture. Incidence was found to be 20-30% in immobilized adults secondary to fractures in 2 case series [47].14 out of our 24 studied patients had deranged kidney function with raised creatinine which is a known risk factor for development of immobilization hypercalcemia. Another limitation of this study may be the variation of vitamin D levels with season. The study period included both winter and summer. Circulating 25(OH)D levels vary seasonally due to seasonal fluctuations in sunlight ultraviolet B irradiation[48].

Conclusion: In this study conducted over a period of 16 months in a tertiary care centre, hypercalcemia due to vitamin D intoxication was found as the leading cause followed by malignancies. As much as possible, we should avoid overtreating vitamin D deficiency.

Table 1.

S.No.	Age/Sex	Serum Calcium (mg/dL)[a]	Serum Albumin (mg/dL)[b]	Serum Calcium corrected (mg/dL)[c]	Serum PTH (ng/L)[d]	Serum Vit D3 (pg/mL)[e]	Diagnosis
1.	57/M	12.4	4.2	12.4	15	26.9	Malignancy lung with bony metastases.
2.	70/M	11.5	4.0	11.5	11	80	Vit D intoxication
3.	70/F	13.2	3.2	13.8	75	76	Hyperparathyroidism with Vit D intoxication.
4.	60/F	12.0	3.3	12.5	28	>150	Vit D intoxication
5.	70/M	11.3	4.2	11.3	21	104	Vit D intoxication with Multiple Myeloma
6.	60/F	11.0	2.5	12.2	18	80	Vit D intoxication with Breast carcinoma.
7.	60/F	11.3	3.6	11.6	39	55	undiagnosed
8.	70/F	11.7	4.0	11.7	14.6	>150	Vit D intoxication
9.	75/F	13.0	4.3	13.0	20	85	Vit D intoxication
10.	60/M	12.8	4.7	12.2	18	>106	Vit D intoxication
11.	55/F	13.0	4.7	12.4	36	40	undiagnosed
12.	65/F	13.3	3.9	13.3	10	78	Vit D intoxication with Carcinoma with unknown primary.
13.	60/M	14.5	2.2	16.4	3.5	95	CNS tuberculosis with Vit D intoxication

14.	60/M	13.2	4.0	13.2	192	8.6	Parathyroid adenoma
15.	80/M	14.0	4.5	14.0	8.6	>150	Vitamin D intoxication
16.	70/M	14.2	4.0	14.2	18	>150	Vitamin D intoxication with hypercalcemic nephropathy
17.	72/M	13.0	4.4	13.0	6	65	Lung squamous cell carcinoma
18.	68/M	18.0	4.2	18.0	2	>150	Vitamin D intoxication .
19.	65/M	15.0	4.2	15.0	4	60	Bronchogenic carcinoma right lung with bony metastases.
20.	44/M	14.6	4.5	14.6	102	40	Primary hyperparathyroidism
21.	55/F	14.0	4.0	14.0	120	10	Primary hyperparathyroidism with vitamin D deficiency.
22.	75/M	14.5	2.9	15.7	6	25	Bronchogenic carcinoma lung with bony metastases.
23.	65/M	15.0	2.2	16.8	10	20	Hodgkins lymphoma.
24.	68/M	12.2	2.4	13.8	11	30	Multiple myeloma.

Note:a. Normal serum calcium= between 8.5 and 10.5 mg/dl (2.2–2.6mmol/L). b. Normal serum albumin=4-5mg/dL. c. Corrected Calcium = (0.8 x[normal serum albumin – Patient's serum albumin])+ serum calcium. d. Normal serum PTH=8-51ng/L. e. Normal serum Vitamin D3=15-75pg/mL.

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