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RESEARCH ARTICLE

CLINICAL PRESENTATION AND ETIOLOGICAL PROFILE OF PATIENTS WITH HYPERCALCEMIA ADMITTED AT A TERTIARY CARE INSTITUTE

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ABSTRACT

Background: Hypercalcemia is a common metabolic abnormality of varying severity that can be adequately diagnosed and treated. Primary hyperparathyroidism and malignant neoplasms are responsible for >90% of all cases.

Objectives: To study the clinical presentation and etiological profile of hypercalcemic patients at a tertiary care institute over a period of 29 months. The number of patients of hypercalcemia due to other rare cause like vitamin D intoxication have been increasing mainly due to over the counter supplementation.

Methods: Thirty subjects 18(60%) females and 12(40%) males with a mean age of 65.5±10.28 with hypercalcemia were studied. The first step in evaluating hypercalcemia was confirming it first, an initial evaluation included the measurement of intact parathyroid hormone and 25-hydroxy vitamin D levels in patients with history of multiple injections of vitamin D.

Results: Out of 30 patients studied, the most common clinical presentation was altered sensorium in 10(33.33%), incidental finding of hypercalcemia in 06(20%) and low back ache with bony pains in 04(13.3%) patients respectively. In etiological profile, the most common etiology was vitamin D intoxication in 11(36.67%) followed by malignancy in 09(30%) and hyperparathyroidism in 06(20%) patients respectively.

Conclusion: In our study vitamin D intoxication (VDI) was the most common cause of hypercalcemia. Inadvertent excessive use of pharmaceutical preparations is the most common etiology of exogenous vitamin D toxicity.

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INTRODUCTION

Hypercalcemia is a common finding in the setting of primary care (Dalemo *et al*., 2012) as well as in emergency departments (Lindner *et al*., 2013) and patients admitted to hospital (Silverberg *et al*., 1995). Primary hyperparathyroidism and malignancy are the two most common causes of increased serum calcium levels, together accounting for about 90% of all cases (Potts *et al*., 2012). Calcium is a critical ion for many physiological processes. Circulating calcium concentrations fluctuate within a narrow range due to the tight regulation of the fluxes at the three main sites of calcium transport (intestine, bone, kidney) mainly by the calciotropic hormones (Shane and Irani, 2006; Parathyroid, 1992; Mundy, 2008).

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Hypercalcemia is a medical condition in which there is excessive calcium in the bloodstream. The normal calcium level ranges from 8.5 to 10.2 mg/dL. A serum calcium of >10.3 mg/dl with a normal serum albumin or ionised calcium of >5.2 mg/dl, defines hypercalcemia. It is divided into three levels: mild (10.5 to 12 mg/dL), moderate (12 to 14 md/dL), and critical (14 mg/dL and above). Those with a mild increase that has developed slowly typically have no symptoms (Minisola *et al*., 2015). In those with greater levels or rapid onset, symptoms may include abdominal pain, bone pain, confusion, depression, weakness, kidney stones, or an abnormal heart rhythm including cardiac arrest (Soar *et al*., 2010). Major reviews correctly point out that the great majority of patients with elevated serum calcium will be found to have either primary hyperparathyroidism or malignancy, although the differential diagnosis is much longer. These other causes of hypercalcemia, including vitamin D intoxication, sarcoidosis, tuberculosis,

some fungal infections, thyrotoxicosis, Addison's disease, milk-alkali syndrome related to the prescription of absorbable alkali and calcium, vitamin A intoxication, therapy with thiazide diuretics or lithium carbonate, familial hypocalciuric hypercalcemia, prolonged immobilization in patients with high skeletal turnover, and the recovery phase of rhabdomyolysis-associated acute renal failure, all amount to fewer than about 10% of all causes of hypercalcemia (Root, 2003). Nevertheless, they are important to consider in certain clinical situations when the underlying cause of hypercalcemia cannot be attributed to primary hyperparathyroidism or overt malignancy. Despite the rather inclusive nature of this list of potential causes of hypercalcemia, there are still other more unusual etiologies reported in single patients or in small groups of patients (Bringhurst *et al*., 2003). Plasma calcium is maintained within the reference range by a complex interplay of 3 major hormones, parathyroid hormone (PTH), 1,25-dihydroxy vitamin D (ie, calcitriol), and calcitonin. These 3 hormones act primarily at bone, kidney, and small intestine sites to maintain appropriate calcium levels. Calcium enters the body through the small intestine and eventually is excreted via the kidney. Bone can act as a storage depot. This entire system is controlled through a feedback loop; individual hormones respond as needed to increase or decrease the serum calcium concentration (Alpern *et al*., 2013). For hypercalcemia to develop, the normal calcium regulation system must be overwhelmed by an excess of PTH, calcitriol, some other serum factor that can mimic these hormones, or a huge calcium load (Blomqvist, 1986).

MATERIALS AND METHODS

This prospective, random-sample study was conducted at the postgraduate department of internal medicine government medical college SMHS hospital Srinagar- a tertiary care center of Jammu and Kashmir. This study included 30 subjects of hypercalcemia studied from january 2015 to july 2017.A proper informed consent was taken before incorporating the subjects into the study. Detailed history, physical examination and laboratory parameters were obtained from the paticipating study subjects.

Diagnosis of Hypercalcemia: The first step in evaluating hypercalcemia was confirming it first, an initial evaluation included the measurement of intact parathyroid hormone and 25-hydroxy vitamin D levels in patients with history of multiple injections of vitamin D. Serum calcium levels were obtained at baseline and in patients with hypercalcemia, the serum calcium levels were reproduced. The adjustment to serum albumin was accomplished as shown below.

Corrected serum calcium was derived from the formula:
Corrected (Ca) = (0.8 x (normal albumin - patient's albumin)) + serum (Ca) level

OR

Corrected (Ca) = Measured (Ca) + {(40 - (albumin)) ×0.02}

The serum levels of PTH were obtained in all patients using CLIA (Chemiluminescence Immunoassays). The suppression or increase levels of PTH hormone in setting of hypercalcemia helped in further evaluation of hypercalcemia. Serum 25-hydroxy vitamin D levels were measured using CLIA assay to diagnose vitamin D intoxications. Bone marrow aspiration/biopsy, serum and urine electrophoresis, skeletal survey in patients with suspicion of multiple myeloma and for the rest, the evaluation was directed towards the etiological agent.

Statistical analysis

The data of demographic profile and biochemical parameters were analyzed with Spss version 20. Qualitative variables were expressed as percentages and the quantitative ones as mean+SD.

RESULTS

In this study, a total of 30 subjects were included,18(60%) females and 12(40%) males with a mean age of 65.5±10.28 (Table 1). The most common clinical presentation was altered sensorium in 10(33.33%) patients followed by incidental finding of hypercalcemia in 06(20%) and low backache with bony pains in 04(13.33%) patients respectively. The other clinical presentations included generalised body aches and cough with weight loss in 02(6.67%) patients each (Table 2). The most common cause of hypercalcemia in our patients was vitamin D intoxication in 11 (36.67%) patients followed by malignancies{Multiple myeloma, carcinoma lung with bony metastasis, carcinoma breast with bony metastasis and Hodgkins lymphoma} in 9(30%) patients, followed by hyperparathyroidism in 06(20%) patients respectively (Table 3).

Table 1. Patient characteristics. Data is presented as mean±SD

Patient characteristic	Mean ± Standard deviation
Age	65.5±10.28
Bilirubin	0.85±0.39
AST	37.4±17.45
ALT	29.1±13.91
ALP	111.86±67.33
Total protein	6.62±0.99
Serum calcium levels	12.72±1.52
Serum phosphate levels	3.42±1.10
Serum albumin	3.14±0.56
Corrected calcium	13.36±1.49
Serum PTH levels	58.29±78.78
25-OH vitamin D3	100.77±136.57

AST: Aspartate Transaminase, ALT: Alanine Transaminase, ALP: Alkaline Phosphatase, PTH: Parathyroid Hormone.

Table 2. Clinical presentation of patients- LBA: Low back ache, LAP: lymphadenopathy

S.no	Clinical Presentation	Number of patients	% age
1	Altered sensorium	10	33.33
2	Incidental finding	06	20.0
3	LBA with bony pains	04	13.33
4	Generalised body aches	02	6.67
5	Bony pains	01	3.33
6	Cough with weight loss	02	6.67
7	Fever with weight loss	01	3.33
8	Hemoptysis with weight loss	01	3.33
9	Fever with LAP	01	3.33
10	Fever with chronic cough	01	3.33
11	Abdominal pain with constipation	01	3.33

DISCUSSION

The most common cause of hypercalcemia in our study was vitamin D intoxication as compared to other studies where

hyperparathyroidism and malignancies accounted for most of cases (14). Primary hyperparathyroidism and malignancy are the two most common causes of increased serum calcium levels, together accounting for about 90% of all cases (Potts and Jüppner, 2012). Mechanisms associated with hypercalcemia are classically divided into parathyroid hormone and non-parathyroid hormone mediated. Parathyroid hormone is the main regulator of calcium homeostasis and its primary increased secretion alters the regulation of serum calcium by acting on different target organs (bone, kidney, gut) (Horwitz *et al*., 2013). Hypercalcemia of non-parathyroid origin is mostly related to production of parathyroid hormone related protein (PTHrP), calcitriol, or cytokines as mediators. Malignancy related hypercalcemia-humoral hypercalcemia of malignancy is a paraneoplastic syndrome resulting from the secretion of parathyroid hormone related protein by the tumour (Shane, 1999). Although any kind of neoplasia may cause the syndrome of humoral hypercalcemia of malignancy, squamous carcinomas are most commonly implicated. Hypercalcemia may be due to local osteolysis, most usually observed in haematological cancers. Overproduction of calcitriol represents the key mechanism in the development of hypercalcemia associated with some forms of malignancy and with granulomatous diseases. Malignant cells and granulomas can over-express 1-α-hydroxylase and increase the conversion of calcidiol to the active form of vitamin D, calcitriol, leading to increased intestinal absorption of calcium, hypercalciuria, and hypercalcemia (Horwitz *et al*., 2013).

Table 3. Etiological Profile of patients – TB; Tuberculosis

S.no	Etiological Profile	Number of patients	%age
1.	Vitamin D intoxication	11	36.67
2.	Hyperparathyroidism	06	20.0
3.	Breast cancer (Ductal cell carcinoma with bony metastasis)	01	3.33
4.	Multiple myeloma	05	16.67
5.	Carcinoma lung (Squamous cell carcinoma) with bony metastasis	02	6.67
6.	Hodgkins lymphoma	01	3.33
7.	Sarcoidosis	02	6.67
8.	Disseminated TB	01	3.33
9.	Thyrotoxicosis	01	3.33

Hypercalcemia leads to hyperpolarization of cell membranes. Patients with levels of calcium between 10.5 and 12 mg per dL can be asymptomatic (Shane, 1999). When the serum calcium level rises above this stage, multisystem manifestations become apparent. Neuromuscular effects include impaired concentration, confusion, corneal calcification, fatigue, and muscle weakness (Solomon *et al*., 1994). Nausea, abdominal pain, anorexia, constipation, and, rarely, peptic ulcer disease or pancreatitis are among the gastrointestinal manifestations. The most important renal effects are polydipsia and polyuria resulting from nephrogenic diabetes insipidus, and nephrolithiasis resulting from hypercalciuria. Other renal effects include dehydration and nephrocalcinosis. Cardiovascular effects include hypertension, vascular calcification, and a shortened QT interval on the electrocardiogram. Bone pain can occur in patients with hyperparathyroidism or malignancy. Osteoporosis of cortical bone, such as the wrist, is mainly associated with primary hyperparathyroidism (Abdelhadi and Nordenstrom, 1998). Excess PTH also can result in subperiosteal resorption, leading to osteitis fibrosa cystica with bone cysts and brown tumors of long bones (Strewler, 2000). Vitamin D is an important prohormone that plays a vital role in calcium homeostasis and bone mineralisation. Vitamin D also subserves in a wide range of fundamental biological functions, such as cell differentiation and the inhibition of cell growth, as well as immunomodulation (Bouillon, 2010). The most commonly available vitamin D supplements consist of 25-hydroxy vitamin D2. In suspected overdose of over-the-counter vitamin D, the level of 25-hydroxy vitamin D3 (not 1,25-dihydroxy vitamin D3) should be measured. Macrophages can cause granuloma- forming (i.e., sarcoidosis, tuberculosis,Hodgkin's lymphoma) increased extra-renal conversion of 25-hydroxy vitamin D3 to calcitriol.PTH levels are suppressed, and levels of 1,25-dihydroxy vitamin D3 are elevated (Dudenkov *et al*., 2015). Hypervitaminosis D is a condition where an increase in the 25-hydroxy vitamin D (25OHD) levels is associated with either hypercalcemia or hypercalciuria, or both. The literature reports that hypercalcemia due to an overdose of vitamin D may appear if serum levels of 25(OH)D reach a range of 150-200 ng/ml (Gupta *et al*., 2014). For this reason, it is generally accepted that serum 25(OH)D level above 150 ng/ml should be observed before a diagnosis of vitamin D toxicity(VDT). VDT may be defined as a state when markedly elevated of 25 (OH)D levels (> 150 ng/mL) coinciding with hypercalcemia, hypercalciuria and very low or even undetectable PTH activity. However, the major clinical worries related to VDT most often focus on elevated calcium levels (hypercalcemia) and a variety of nonspecific symptoms (Agraharkar *et al*., 2012). Vitamin D toxicity involves an increased concentration of vitamin D metabolites reaching the vitamin D receptor (VDR) in the nucleus of target cells and causing exaggerated gene expressions. The three mechanisms are suggested to explain vitamin D toxicity (Gupta *et al*., 2014; Jones, 2008).

1. Toxicity mediated by the increased levels of plasma 1,25(OH)2D (active hormonal form of vitamin D) leads to its increased intracellular concentration. This hypothesis is not strongly supported, as only Mewar *et al*. reported elevated 1,25(OH)2D levels, and many other studies revealed that 1,25(OH)2D levels were only marginally elevated or normal.
2. 1,25(OH)2D has low affinity to the vitamin D binding protein (DBP, transport protein) and high affinity to VDR making it an important ligand with access to the transcriptional signal transduction machinery. At the state of hypervitaminosis D, the levels of various vitamin D metabolites are markedly increased compromising the capacity of the DBP, and in turn enable other vitamin D metabolites to enter the cell nucleus. Among these inactive metabolites 25(OH)D has the strongest affinity to the VDR, so at high concentrations 25(OH)D itself may stimulate transcription.
3. Vitamin D intake raises the concentration of many vitamin D metabolites especially vitamin D itself and 25(OH)D. In hypervitaminosis D, vitamin D metabolites such as vitamin D3, 25(OH)D3, 24,25(OH)2D3, 25,26(OH)2D3 and 25(OH)D3-26,23-lactone increase significantly. These concentrations exceed the DBP binding capacity and cause release of free 1-alpha 25(OH)2D3, the latter one enters target cells. The various studies and reports of vitamin D intoxication indicate that plasma 25(OH)D3 is a good biomarker for toxicity.

The diagnosis of VDT can be made on clinical grounds. Detailed clinical and drug history are of paramount importance

in order to make early diagnosis. Most patients who are suffering from VDT take vitamin D for osteoporosis, hyperparathyroidism, hypophosphatemia, osteomalacia, or renal osteodystrophy in excessive dosages or at too frequent dosing intervals. With the recent idea that vitamin D is protective of many diseases, vitamin D therapy became very widespread in otherwise normal subjects. Laboratory tests in patients with symptomatic VDT will show an elevated serum and urine level of calcium and reduced serum level of parathormone (intact), serum 25(OH)D3 level > 100 ng/ml, and normal or decreased 1,25(OH)2D levels (Gupta *et al*., 2014; Agraharkar *et al*., 2012; Potts and Jüppner, 2012). Treatment for vitamin D toxicity includes: discontinuing intake, a diet with low calcium and phosphorus content, intravenous (IV) hydration, loop diuretics, glucocorticoids, and calcitonin (Besbas *et al*., 1989). More recently, oral and IV bisphosphonates have been proven to be effective in the treatment of VDT (Doneray *et al*., 2008). IV hydration and diuretics are used for mild cases. Patients with moderate and severe hypercalcemia must be followed closely after being hospitalized. When the calcium level exceeds 12 mg/dl, dehydration develops. The hydration used for treatment increases the glomerular filtration, which leads to calcium being filtered out of the system through the glomeruli (Gurkan *et al*., 2004). Loop diuretics such as furosemide and ethacrynic acid, added to the treatment after hydration, inhibit the reabsorption of urinary calcium, and reduce the calcium level by increasing urinary calcium excretion. In patients with severe hypercalcemia, IV hydration and diuretic treatment should be accompanied by glucocorticoids, calcitonin or preferably bisphosphonate treatment. Glucocorticoids suppress the activity of calcitriol, and reduce the production of 1,25(OH)2 D2 and intestinal absorption of calcium. In addition, reabsorption through the renal tubules is prevented, facilitating the renal excretion of calcium. The effects are observed 24-72 hours after the start of treatment. Prednisolone, at a dose of 1-2mg/kg/day, can be administered orally in divided doses (Atabek *et al*., 2006; Barrueto *et al*., 2005).Calcitonin inhibits osteoclast activity and reduces bone resorption by increasing urinary calcium excretion. Calcitonin, at a dose of 2-4 IU/kg/dose, is administered subcutaneously in 2-4 doses. It is effective over a period of 2-4 hours and has a low risk of side effects. Intermittent administration is recommended due to the development of resistance (tachyphylaxis) after its initial rapid effects (Alikasifoglu, 2008). Following hydration and diuretics, IV or oral bisphosphonates should be started in persistent cases. Bisphosphonates lead to osteoclast apoptosis by binding to the cell surface membrane. In addition to their effects on the lifespan of osteoclasts, they also inhibit osteoclast-induced bone resorption. The half-life of bisphosphonates is less than several hours and they are rapidly excreted from the circulation. Therefore, medications such as pamidronate are administered at a dose of 0.5-1 mg/kg/dose by IV infusion (Doneray *et al*., 2009). Since recurrent hypercalcemia may develop, hemodialysis is the preferred treatment in patients with hypercalcemic crisis and acute and/or chronic renal failure (Alikasifoglu, 2008).

Conclusion

In our study Vitamin D intoxication (VDI) was the most common cause of hypercalcemia. There are many forms of exogenous (iatrogenic) and endogenous vitamin D toxicity. Inadvertent excessive use of pharmaceutical preparations is the most common etiology of exogenous vitamin D toxicity. Endogenous etiologies may result from ectopic production of 1,25 (OH)D2 in granulomatous diseases, such as sarcoidosis and tuberculosis, or in lymphoma.

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Conflicts of interest: None

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