The changing profile of hypercalcemia in a tertiary care setting in North India: an 18-month retrospective study

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Summary

This retrospective study was undertaken to determine the profile of hypercalcemia in all patients who presented to Medanta-The Medicity, a tertiary care hospital in North India. A total of 255,830 patients presented to the hospital during 1 st January 2014 till 30 th June 2015 (18 months). Among them calcium measurement was done in 26,297 (10.2%) patients. A total of 552 patients was found to have hypercalcemia. Among them, 15 (2.7%) patients had transient hypercalcemia and 537 (97.3%) had sustained hypercalcemia. The incidence of hypercalcemia was 2.09%, being transient in 0.05% and sustained in 2.04%. The most common causes in the sustained group were malignancy (23.1%) followed by primary hyperparathyroidism (PHPT, 21.9%). Most cases of PHPT were asymptomatic. Interestingly, we found emergence of two unusual groups of hypercalcemia, namely hypercalcemia of advanced chronic liver disease (n = 34) and vitamin D toxicosis (n = 21) in the non-parathyroid group of hypercalcemia. This changing pattern of hypercalcemia should be kept in mind while evaluating a patient of hypercalcemia in a hospital setting.

KEY WORDS: hypercalcemia; malignancy; hypervitaminosis D; vitamin D toxicosis; chronic liver disease; granulomatous disease; thyrotoxicosis.

Introduction

Hypercalcemia is a relatively common condition in hospital populations. The most common reasons for hypercalcemia in any hospital setting are malignancies, followed by symptomatic PHPT, granulomatous diseases and other uncommon causes. The advent of rapid and reliable automated methods for measuring serum calcium makes it possible to detect hypercalcemia early in the course of the disease process, even when patients are asymptomatic or when patients are evaluated for unrelated conditions. Calcium estimations are made on routine blood analysis in a significant number of patients that are evaluated in our hospital. We intended to look into the profile of hypercalcemia among patients that presented to our hospital and the frequency distribution of its causes.

Materials and methods

All calcium measurements done on patient’s sera over the period between 1 st January 2014 and 30 th June 2015 were retrieved from the Hospital Information System (eHIS) by the Information Technology department. Subjects of the study came from the outpatient clinics, hospital in-patients and emergency department of Medanta-The Medicity, a tertiary care center in North India.

The hospital measures serum total calcium on an automated analyzer (Roche Hitachi 912 Chemistry Analyzer, Boehringer Mannheim, Germany). Serum calcium was analyzed using O-cresolphthalein dye-binding technique. Serum 25-hydroxy vitamin D (25OHD) and intact parathyroid hormone (iPTH) levels were measured by the electro-chemiluminescence immunoassay (ECLIA) on cobase-e411 immunoassay analyzer.

The actual number of patients investigated for calcium status was determined. The initial serum calcium done on each patient was used to categorize hypercalcemia (serum total calcium of > 10.4 mg/dL in adults and > 10.8 in children below 5 years of age). All cases were categorized into two groups: (i) transient hypercalcemia and (ii) sustained hypercalcemia.

The incidence of hypercalcemia was calculated using both the transient and sustained cases whereas the frequency distribution of causes was estimated separately in each group. Sustained group was further categorized into PTH-dependent and PTH-independent groups. The PTH-independent group is further sub-classified depending upon the etiologies for hypercalcemia. The data is expressed as numbers, percentages, standard deviations and ranges whichever applicable.

Results

A total of 255,830 patients was registered in our hospital in a period of 18 months (January 1 st 2014 till June 30 th 2015). Serum calcium estimation was done in 26,297 (10.2%) patients. Among them, 16,684 (63.5%) presented in outpatient clinics, 8,862 (33.7%) as in-patients and 751 (2.8%) as emergency patients. A total of 552 patients was found to have hypercalcemia, among them 347 (62.8%) were in-patients and 205 (37.2%) were out-patients. The mean age of all patients who had hypercalcemia was 55.2 years ± 17.9 (range 1.0 - 94.0 years), 322 patients being males (mean age 55.2 years ± 17.9, range 1.0 - 94.0 years) and 230 being females (mean age 55.7 years ± 17.1, range 2.0 - 88.0 years). Fifteen (2.7%) patients had transient hypercalcemia...
(one calcium reading above 10.4 mg/dL followed by at least 2 readings in normal range) and 537 (97.3%) had sustained hypercalcemia (serum calcium above 10.4 mg/dL on more than two occasions). The incidence of hypercalcemia was 2.09%, being transient in 0.05% and sustained in 2.04%.

A total of 157 (29.2%) patients was found to have PTH-dependent hypercalcemia (hypercalcemia in presence of unsuppressed PTH levels). The mean age of patients was 56.3 years (range, 2.0 – 94.0 years), 79 being females (mean age, 55.5 years; range, 2.0 – 88.0 years), and 78 being males (mean age, 57.2 years; range, 14.0 – 94.0 years). Among them 98 (62.4%) patients were subsequently found to have one or more parathyroid adenomas on imaging (ultrasonography of parathyroids and sest-MIBI scan of parathyroids). Most of the patients (n = 83, 84.6%) had no characteristic hyper-parathyroid bone disease and/or kidney stones. None had brown tumors. Eight (5.0%) patients had tertiary hyperparathyroidism (established chronic kidney disease, hypercalcemia and hyperparathyroidism). Two patients were diagnosed as Multiple Endocrine Neoplasia type 1 syndrome (MEN 1). In eighteen (11.4%) patients, the lesions were not localized and were put on follow up. Thirty one (19.7%) patients were not evaluated, as they had come for other problems and got discharged without further evaluation for hypercalcemia.

A total of 380 (70.7%) patients was found to have PTH-independent hypercalcemia. The mean age of patients was 54.6 years (range, 2.0 – 92.0 years). 246 were males (mean age, 55.5 years; range, 2.0 – 92.0 years), and 124 were females (mean age, 55.4 years; range, 2.0 – 88.0 years). Among this group, malignancy was diagnosed as cause for hypercalcemia in 124 (32.6%) patients. The mean age was 59.9 years (range, 26.0 – 92.0 years), 89 being males (mean age, 61.7 years; range, 31.0 – 92.0 years), and 35 being females (mean age, 54.9 years; range, 26.0 – 75.0 years).

Hypercalcemia of advanced CLD was diagnosed as cause for hypercalcemia in 34 (8.9%) patients. The mean age was 48.1 years (range 3.0 – 69.0 years), 24 were males (mean age, 50.9 years; range, 26.0 – 66.0 years), and 12 were females (mean age, 42.7 years; range, 3.0 – 69.0 years). All the patients had advanced CLD (established cirrhosis, Child class B or C, decompensation with variceal bleed, ascites with or without spontaneous bacterial peritonitis, or encephalopathy).

Vitamin D toxicosis was diagnosed in 21 (5.5%) patients. The mean age of patients was 59.7 years (range, 2.0 – 87.0 years), 12 were males (mean age, 58.1 years; range, 2.0 – 87.0 years), and 9 were females (mean age, 59.7 years, range, 3.0 – 83.0 years).

Granulomatous disease was diagnosed as cause for hypercalcemia in 20 (5.3%) patients. The mean age was 54.3 years (range, 10.0 – 87.0 years). Males were 12 (mean age, 55.3 years; range, 10.0 – 87.0 years), and 8 were females (mean age, 48.2 years; range, 17.0 – 80.0 years). Thyrotoxicosis was diagnosed in 5 (1.3%) patients (4 females and 1 male). 176 (46.3%) patients of non-parathyroid hypercalcemia group could not be sub-classified further as the data was not available. Most of those patients had come for management of other conditions like selected surgeries and preferred not to be evaluated further for hypercalcemia.

Figure 1 shows the flow chart of the study.

**Discussion**

The incidence of hypercalcemia in our study was 2.09%, being transient in 0.05% and sustained in 2.04%. The incidence of hypercalcemia in hospital populations varies from 0.17 to 2.92% (1-4).

Hypercalcemia occurs in up to 30% of patients with malig-
nancy (5). This is the most common group of hypercalcemia in the hospital setting. The malignancies most commonly associated with hypercalcemia are epidermoid malignancies (squamous cell lung carcinoma, urethral cancers, head and neck cancers), multiple myeloma, breast cancer, renal cell carcinoma and lymphoma (6, 7). In our study, this group accounted for 23.1% cases of sustained hypercalcemia. The frequency distribution of malignancy-associated hypercalcemia is given in Table 1. The frequency of the pattern of malignancies is hospital-specific, as it depends upon the oncologic services available in the hospital.

In our data, the second most common cause of hypercalcemia was PHPT (21.9%), including 98 surgically proven PHPT, two MEN 1 syndromes, 18 patients of biochemical PHPT but no parathyroid lesions on imaging. There is a changing pattern of PHPT in India. Previously symptomatic PHPT was predominantly seen in tertiary care settings especially in North India. Mishra et al. studied 29 consecutive PHPT patients prospectively in 2001. All patients had osteitis fibrosa cystica and 20 cases (69%) had brown tumors (8). Bhansali et al. in 2005, in a retrospective study of 13 years, found bone disease in 46% PHPT patients and renal stones in 21% patients (9). Priya et al. in 2008 studied 39 PHPT patients and found brown tumors in 58%, renal stones in 42% and nephrocalcinosis in 12% patients (10). Mithal et al. in 2015 reported 50 PHPT patients. None of the patients had brown tumors or bone deformities (11). All the aforementioned studies of PHPT are from tertiary care settings of North India. These studies demonstrated that the incidence of bone disease and renal stones have decreased in India over last 15 years.

A significant proportion of patients with decompensated CLD develop hypercalcemia in the course of the disease. Previously, we published two cases of hypercalcemia of advanced CLD who were extensively evaluated. They had no other cause of hypercalcemia except for advanced CLD (12). There were 34 patients with advanced CLD, who developed hypercalcemia in this retrospective study of 18 months. There were no other causes for hypercalcemia except for the liver disease per sé. Hepatic malignancy was ruled out in all the patients by appropriate biochemical tests and imaging. Gerhardt et al. described the same pattern of hypercalcemia in 11 patients who had advanced CLD but no hepatic cancer (13). Hypercalcemia caused by advanced CLD without hepatic neoplasia is a poorly understood condition. The unique feature of this type of hypercalcemia is its transient nature that may or may not require treatment. Our hospital has a large volume liver transplant programme in India and during the studied 18 months, about 450 liver transplantations were performed. This group of non-parathyroid hypercalcemia is not uncommon in any tertiary care center where there is advanced hepatology unit and active liver transplantation programme.

Hypercalcemia secondary to hypervitaminosis D is an interesting group of hypercalcemia in a tertiary care setting. This entity was considered rare a few decades ago. Increasing interest in vitamin D supplementation has led to a surge in vitamin D prescription in recent years. Overzealous correction of low serum 25(OH)D levels in individuals not having metabolic bone disease has led to the emergence of an increasing number of cases of vitamin D toxicity over recent years. Joshi, in 2009 reported hypercalcemia due to hypervitaminosis D in 7 children aged 7.5 to 25 months, due to prescription of large doses of vitamin D for wrong indications (14). Koul et al. reported vitamin D toxicity in 10 adults in 2011, from Kashmir, India (15). Previously we reported a case series of 15 patients with symptomatic hypercalcemia secondary to hypervitaminosis D in one of tertiary hospitals of North India. All the patients experienced toxicity due to excessive administration of vitamin D by oral and/or parenteral route (16). Recently, we reported another case series of 16 patients with vitamin D toxicity seen between January 2011 and January 2013 and discussed in detail the clinical presentation, risk factors, management and prevention of vitamin D toxicity (17). In the present study, a total of 21 patients had hypercalcemia in presence of suppressed PTH and elevated levels of serum 25(OH)D (>150 ng/mL). There was no other cause for non-parathyroid hypercalcemia in these patients. All of them had received parenteral vitamin D preparations (multiple 600,000IU preparations for intra-muscular injection) except for one who had taken oral cholecalciferol 60,000IU daily for more than three months. Most of them were treated with fluids, calcium/vitamin D restriction and steroids. In some of them, hypercalcemia persisted for many months. Over years, this group has become important cause of non-parathyroid hypercalcemia in hospital settings.

Harrell and Fisher established the association of hypercalcemia and granulomatous disease in 1939 (18). Various granulomatous diseases associated with hypercalcemia are sarcoidosis (19), tuberculosis (20), leprosy (21), beri-beri and disseminated candidiasis (22). In our study, granulomatous diseases were responsible for 5.3% cases of non-parathyroid hypercalcemia. Tuberculosis was diagnosed in 14 patients. Among them, 6 had miliary tuberculosis, 5 had tuberculosis of pulmonary system and 3 had tuberculosis of the gastrointestinal system. Six patients were detected to have sarcoidosis with mediastinal lymphadenopathy (n = 3); cutaneous sarcoidosis (n = 2) and 1 patient had only hypercalcemia as a feature of sarcoidosis. Due to decline in the prevalence of tuberculosis and leprosy in the western nations, hypercalcemia caused by these two diseases also declined. However, in under-developed nations, these chronic infective granulomatous diseases still contribute significantly to the non-parathyroid group of hypercalcemia.

In this study, 5 patients with PTH-independent hypercalcemia were caused by thyrtoxicosis. Four of them were diagnosed with Graves’ disease and 1 with toxic adenoma. Thyrotoxicosis due to Graves’ disease, toxic multinodular goiter, toxic adenoma and subacute thyroiditis can cause hypercalcemia (23). Thyrotoxicosis was believed to cause mild

<table>
<thead>
<tr>
<th>Malignancies</th>
<th>Number (%)</th>
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</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>32 (25.8)</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>20 (16.1)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>20 (16.1)</td>
</tr>
<tr>
<td>Lung malignancies</td>
<td>15 (12.1)</td>
</tr>
<tr>
<td>Skin</td>
<td>14 (11.3)</td>
</tr>
<tr>
<td>Urogenital</td>
<td>11 (8.9)</td>
</tr>
<tr>
<td>Breast</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Brain</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Bone</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Unknown Primary</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

Table 1 - Frequency distribution of malignancy-associated hypercalcemia.
to moderate degree of hypercalcemia (24, 25), and severe hypercalcemia was considered rare (26). However, many reports of severe hypercalcemia caused by thyrotoxicosis have been published (27, 28). In our study, the highest serum total calcium of one thyrotoxic patient (Graves’ disease) was 13.4 mg/dL and other 4 patients had serum total calcium levels below 13 mg/dL.

A large group of non-parathyroid hypercalcemia patients (n = 176) could not be sub-classified further. As the hospital provides tertiary care, patients visit here for specific reasons like cardiac services, neurological services, gastroenterological and hepatological services, etc., from far off areas and from different nations. This group of patients had come to the hospital for other health conditions. In the process, they had also been detected to have non-parathyroid hypercalcemia. Their further evaluation is unavailable, as the patients did not prefer to get further investigated for hypercalcemia. Furthermore, 24 patients in this group were on thiazides, but whether that was the reason for hypercalcemia could not be ascertained.

Our study has certain limitations that need to be mentioned. First of all, this is a retrospective study. We could not collect albumin-corrected calcium or ionized calcium data. Our hospital is a large volume tertiary care center where some services are well developed than others, like cardiac services, gastroenterological services, hepatology and liver transplantation services, etc. The incidence of hypercalcemia in our hospital may not be generalized. For instance, large number of hypercalcemia of advanced CLD may be seen only in hospitals where advanced hepatology and liver transplant programme is available. Another limitation of our study is that a large number of patients could not be evaluated adequately. Thirty-one patients in the PTH-dependent group and 176 patients in the non-parathyroid group were not evaluated in this hospital after diagnosis of hypercalcemia. Despite these limitations, this is an important 18 months data showing emergence of two relatively unknown causes of hypercalcemia in a tertiary care setting.

Conclusion

This 18-month retrospective study reveals that the profile of hypercalcemia is changing in tertiary care settings in North India. Malignancy-associated hypercalcemia is the largest group as has always been in any hospital setting. PHPT is changing in that more and more patients are asymptomatic compared to previous studies in developing countries where symptomatic PHPT predominated. Vitamin D toxicity is not uncommon these days, especially in under-developed nations where parenteral vitamin D preparations are available over-the-counter. Furthermore, the poorly reported hypercalcemia of advanced CLD is seen frequently in a tertiary care hospital with large volume gastroenterological services. Chronic infective granulomatous diseases like tuberculosis still contribute significantly to the non-parathyroid group of hypercalcemia in India. Clinicians should be aware of these changing patterns of hypercalcemia in hospital settings.

Disclosure

The Authors of this manuscript have no conflicts of interest to disclose.

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References

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