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Addressing Hypercalcemia: A 3-Year Retrospective Analysis in a Tertiary Care Center

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ABSTRACT

Hypercalcemia is a significant electrolyte disorder and might be seen as the first finding of an occult disease. This study aimed to assess the clinical features of patients with hypercalcemia, to identify the underlying causes and to determine whether physicians undertook further diagnostic investigations to facilitate advanced diagnosis.

Between July 2014 and June 2017, patients with total corrected calcium levels≥11 mg/dl, aged 18 and older were included in this study. The patients' data collection was evaluated retrospectively.

516 patients were evaluated for hypercalcemia. 35.9% had primary hyperparathyroidism (PHPT), 33.9% had hypercalcemia of malignancy (HCM) and 12.8% were found to have drug-induced hypercalcemia. Patients with HCM had significantly higher calcium levels than patients with PHPT, tertiary hyperparathyroidism, and drug-induced hypercalcemia (p=0.001, p=0.017, p=0.001, respectively). Multiple myeloma (27.4%) was the most frequent malignancy-caused hypercalcemia, followed by lung (18.9%) and breast cancer (9.1%).

Our findings indicate that diagnostic tests may be inadequate, particularly in asymptomatic and/or mild-to-moderate cases. It is essential to evaluate clinical indicators and consider drug-induced hypercalcemia, which is notably prevalent in our study. Recognizing the possibility of multiple concurrent causes, including malignancy, drug use, and primary hyperparathyroidism (PHPT), is vital for effective management.

Keywords: Calcium, Hypercalcemia, Malignancy, Hyperparathyroidism, Adverse drug reactions

Introduction

The total serum calcium level is calculated by correcting the measured value according to albumin. Normal corrected calcium values are generally given as 8.5-10.5mg/dl (2.1- 2.5mmol/l) (1,2). However, since reference values may vary between laboratories, hypercalcemia is defined as an albumin-corrected serum total calcium higher than the upper limit determined for that laboratory. The diagnosis should be made when calcium elevation persists in repeated measurements (3). It may be symptomatic or asymptomatic, usually correlated with calcium levels, and may be the first finding of an occult disease (4).

The first step in the differential diagnosis is to measure parathyroid hormone (PTH) to differentiate PTH-mediated hypercalcemia. High and normal PTH levels in a hypercalcemic patient suggest hyperparathyroidism, whereas suppressed PTH levels should suggest other differential diagnosis (5). Primary hyperparathyroidism (PHPT) and malignancy account for more than ninety percent of hypercalcemia cases (1,6–9). In most cases, patients presenting with asymptomatic or mild symptoms are detected incidentally during laboratory tests (6,10).

Although PHPT is the most common cause of hypercalcemia, a study conducted in the outpatient clinics of a tertiary care hospital showed that PTH levels were checked in only one-third of hypercalcemic patients. Testing was performed more often when calcium levels exceeded 12 mg/dl. (11). A number of studies have demonstrated that the most prevalent cause of hypercalcemia among hospital-based patients is malignancy (12–15).

In our country, several studies have investigated hypercalcemia in pediatric patients, internal

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medicine wards, and emergency departments. However, hospital-based data in adults remain limited (16–18).

This study aimed to assess the clinical features of patients with hypercalcemia, to identify the underlying causes and to determine whether physicians undertook further diagnostic investigations to facilitate advanced diagnosis.

Materials and Methods

All results with serum total calcium levels of 10.5mg/dl and above in biochemistry examinations between July 2014 and June 2017 were obtained from the Hospital System Analysis unit. Repeated results of the same patients, patients under 18 years of age, and patients without concurrent serum albumin were excluded from the study. In the remaining patients, corrected calcium was calculated with the following formula: [4-plasma albumin(g/dl)]x0.8+serum calcium (mg/dl) (2). Patients with persistent hypercalcemia (as identified by at least two distinct laboratory test results) whose corrected calcium level was 11 mg/dL or above were included in the study. Patients with a corrected calcium level above 10.6 mg/dl, which is the upper limit of our hospital laboratory, and below 11mg/dl were excluded due to lack of data. Corrected calcium levels above the normal value for our laboratory and <12mg/dl (<3mmol/L) were classified as mild, ≥12mg/dl and <14mg/dl (3-3.49mmol/L) as moderate, ≥14mg/dl (≥ 3.5mmol/L) as severe hypercalcemia (2,6,9,19–22).

Age, gender, and main presenting complaints and/or findings were recorded from the Hospital Information Management System; Probel. Calcium, albumin, phosphorus, creatinine, estimated glomerular filtration rate (eGFR), PTH, ALP, TSH, sT4, 25(OH)vitamin D levels were investigated retrospectively. Biochemical data were analyzed on a Beckman Coultier device. eGFR was calculated by the central laboratory automation system using the MDRD formula. Intact PTH was measured on a Beckman Coultier LH device. Vitamin 25(OH)D was measured by immunoassay method using chemiluminescence microparticle immunometric method (CMIA) technology on a Siemens Advia Centaur device.

We recorded the presence of nephrolithiasis, imaging findings of bone metastases, malignancy pathology results, and the need for hospitalization for diagnosis or treatment of hypercalcemia.

The diagnosis registered on the system as the etiology of hypercalcemia were compared with the available data. Patients with insufficient investigations were clasified as undiagnosed, even if they were under follow-up for a presumed a diagnosis. PTH-related peptide (PTHrP) level cannot be analyzed in our hospital. Therefore, among patients diagnosed cancer and registered as hypercalcemia of malignancy (HCM) on the hospital system, those with low PTH levels and with bone metastases were accepted as HCM.

Statistical Analysis: All analyses were performed in SPSS (Statistical Package for the Social Sciences) 22.0 package program. Frequency and percentage, mean value, standard deviation, median, highest and lowest values are presented as descriptive statistics. Shapiro Wilk and Kolmogorov Smirnov tests were used to check the normal distribution of the data. Chi-Square, Fisher's and Monte Carlo exact tests were used when necessary to analyze the variables specified by counting. Since the data were not normally distributed, Mann Whitney U Test was used for pairwise group comparisons, Kruskal Wallis analysis was used for comparisons between more than two groups and Dunn-Bonferroni test was used as a multiple comparison test. A p-value<0.05 was considered as statistically significant.

The study was approved by Ethics Committee on February, 1, 2018, with decision number 2018/03-13.

Results

A total of 11415 biochemistry results with total calcium ≥10.5mg/dl were analyzed. We identified 754 patients aged 18 years and older with a corrected calcium value of 11mg/dl or more. Of these patients, 111 were excluded from the study because the control calcium level was <11mg/dl. In 57 patients, calcium measurements were not repeated, and 70 patients were not subjected to further investigation despite persistent hypercalcemia. In conclusion, 127 (19.8%) of 643 patients with calcium ≥11mg/dl were not further investigated for various reasons. Therefore, they were not included in the statistical analyses for diagnostic approach and etiology (Figure 1).

516 patients were included in the statistical analysis. 59.7% of the patients were female. The age at diagnosis of hypercalcemia varies between 18 and 94 years. The mean age of female patients was 61.3±14.296 and male patients was 62.24±14.001.

Table 1: Hospital Admission Symptoms and/or Findings of The Patients

	n (%)
Neurological	
Fatigue/Weakness	56 (10.9)
Altered mental status	19 (3.7)
Cramp	1 (0.2)
Total	76(16.8)
Skeletal System	
Bone pain	53 (10.3)
Osteoporosis	2 (0.4)
Total	55 (10.7)
Gastrointestinal System	
Constipation	18 (3.5)
Appetite loss	9 (1.7)
Nausea-vomiting	9 (1.7)
Abdominal Pain	5 (1)
Pancreatitis	3 (0.6)
Total	44 (8.5)
Urinary System	
Nephrolithiasis/ flank pain	9 (1.7)
Polyuria/polydipsia	6 (1.2)
Acute renal failure	4 (0.8)
Total	19 (3.7)
Other**	13 (2.5)
Unknown symptom status	19 (3.7)
Asymptomatic	301 (58.3)
Total number of patients	516

* Patients with more than one symptom/finding were included under the relevant headings.
** Combination of symptoms including anxiety, discomfort, restlessness, difficulty in focusing.

Table 2: Classification of Patients According To Underlying Diagnosis For Hypercalcemia

Diagnosis	n(%)
Primary hyperparathyroidism	185 (%35.9)
Hypercalcemia of malignancy	175 (%33.9)
Drug-induced hypercalcemia	66 (%12.8)
Tertiary hyperparathyroidism	22 (%4.3)
Other	
Sarcoidosis	5 (%1)
Familial hypocalciuric hypercalcemia	2 (%0.4)
Tuberculosis	1 (%0.2)
Hyperthyroidism	1 (%0.2)
Granulomatous disease secondary to CVID	1 (%0.2)
Undiagnosed patients	58 (%11.2)
Total	516 (%100)

CVID: Common Variable Immune Deficiency

Table 3: Calcium Levels Based on The Diagnosis of The Patients

Diagnosis	Median (Min- Max)	*p
Primary hyperparathyroidism (n:185)[a]	11.5 (11.0-15.7)	
Hypercalcemia of malignancy (n:175)[b]	13.4 (11.1-19.9)	
Drug-induced hypercalcemia (n:66)[c]	11.9 (11.1-15.1)	
Tertiary hyperparathyroidism (n:22)[d]	12.1 (11.0-14.7)	
Other (n:10)e	12.4 (11.0-17.4)	p=0.001
Total (n:458)	12.2 (11.0-19.9)	

SD: Standard deviation
p=0.003 between groups a and d**
p=0.001 between groups b and a,c,d**
p=0.011 between groups a and c**
There is no significant difference between other groups
**Dunn-Bonferroni test
*Kruskal Wallis test p=0.001

Table 4: Underlying Diagnosis of Patients With Hypercalcemia of Malignancy

Diagnosis	Number of patients n (%)
Hematological malignancies	60 (34.3)
Multiple myeloma	48
Diffuse large B cell lymphoma	7
Other lymphoma types	4
Leukemia	1
Lung cancer	33 (18.9)
Breast cancer	16 (9.1)
Head and neck cancers	8 (4.6)
Genitourinary system cancers	16 (9.1)
Urinary system cancers	12
Endometrial/cervix cancer	2
Prostate cancer	2
Gastrointestinal system cancers	19 (10.9)
Esophageal/Stomach/Colorectal cancers	9
Pancreatic cancer	7
Liver and cholangiocellular cancer	3
Other	12 (6.8)
Metastatic carcinoma of unknown primary origin	6
Skin cancer	3
Soft tissue sarcoma	2
Central nervous system tumor	1
Without tissue diagnosis	11 (6.3)
Total	175 (100)

Data about symptoms and/or findings of 3.4% (n:19) of the patients could not be accessed through the hospital system. In 58.3% of the patients, hypercalcemia was detected incidentally or they were admitted for unrelated reasons and considered asymptomatic. In symptomatic patients the most common presenting symptoms were neurologic complaints (16.8%). Among these, the most common was fatigue and/or weakness (10.9%). The second most common complaint was skeletal system related (10.7%). The presenting symptoms and/or findings of the patients are shown in detail in Table 1.

Table 5: Drugs That Cause Hypercalcemia

Drug name	Number of patients (n)	%*
Calcitriol	49	74.2
Calcium acetate/ Calcium carbonate	26	39.4
Cholecalciferol	12	18.2
Calcium levulinate	4	6.1
Thiazide diuretics	1	1.5

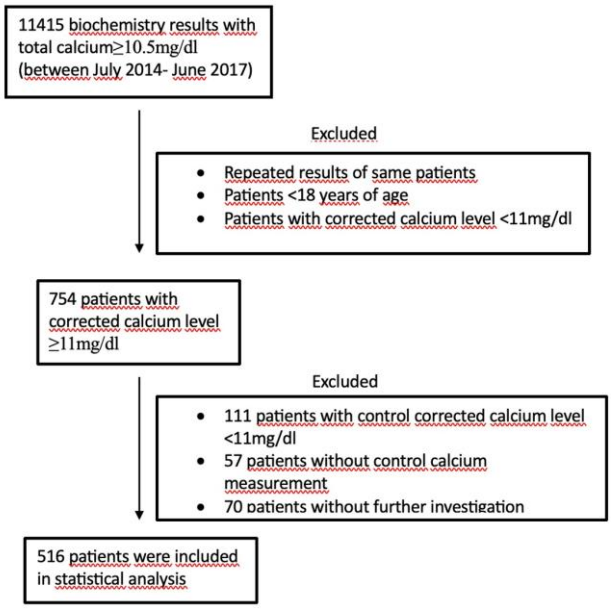

Fig. 1. Flow chart of the study

Of the 516 patients, 237 (45.9%) had mild, 209 (40.5%) had moderate and 70 (13.6%) had severe hypercalcemia. Data about the symptoms of 497 patients were available and those patients were analyzed according to the degree of hypercalcemia. 74.3% of patients with mild hypercalcemia were asymptomatic, while 60.9% of patients with severe hypercalcemia were symptomatic. The frequency of being symptomatic increased significantly as the severity of hypercalcemia increased (p=0.001).

The most common diagnosis was PHPT in 35.9% (n:185) of the patients. The second most common cause was HCM in 33.9% (n:175) and the diagnosis could not be clarified in 11.2% (n:58) of the patients. The distribution of diagnosis is shown in Table 2.

The frequency of the female gender (n:153, 82.7%) was significantly higher in patients with PHPT (p=0.001). Male gender (62.9%, n:110) frequency was significantly higher in patients diagnosed with HCM (p=0.001).

Among the patients, 54.7% (n:282) were hospitalized for further investigation and/or treatment. The most common diagnosis in inpatients was HCM (54.3%, n:153), followed by PHPT (15.2%, n:43). In outpatients, the most common diagnosis were PHPT (60.7%, n:142), drug-induced hypercalcemia (15.8%, n:37) and HCM (9.4%, n:22).

The mean calcium levels of the diagnostic groups are shown in Table 3. A statistically significant association was found between the diagnosis groups and calcium levels (p=0.001). Patients with HCM had significantly higher calcium levels than patients with PHPT, tertiary HPT, and drug-induced hypercalcemia (p=0.001, p=0.017, and p=0.001, respectively). In the assessment of the hypercalcemia severity in diagnostic groups, the frequency of mild hypercalcemia was significantly higher in PHPT (p=0.001) and significantly lower in HCM (p=0.001). There was no significant difference in other diagnostic groups based on the severity of hypercalcemia.

The PTH levels of PHPT patients ranged from 36pg/ml to 1278pg/ml. Parathyroidectomy was indicated in 68.7% (n:127) of patients with PHPT. Of those, 93 patients underwent parathyroidectomy. Out of the 78 patients whose data could be accessed through the hospital system, 70 had a single adenoma, three had multiple adenomas, two had hyperplasia in more than one gland, one had an atypical adenoma and one had parathyroid carcinoma. Pathology showed normal parathyroid tissue in one patient. Investigation is ongoing for ectopic parathyroid tissue, as this patient continued to have postoperative hypercalcemia. Among the patients diagnosed with primary hyperparathyroidism (PHPT), seven had multiple endocrine neoplasia (MEN)- five with MEN1 and two with MEN2A. Pathology reports revealed that three of these patients had a single adenoma, two had multiple adenomas, and one had parathyroid hyperplasia. The pathology report for one patient could not be accessed as the surgery was performed in another hospital. Additionally, 10.3% (n:19) of all PHPT patients had a concurrent malignancy diagnosis.

The mean PTH level In the HCM group was 27.23±47.41pg/ml. However, PTH level was not measured in 45.7% (n:80) of these patients, and possible concomitant PHPT was not evaluated. Hematologic malignancies (34.3%, n:60) were the most common diagnosis, followed by lung cancer (18.9%, n:33). The distribution of patients according to malignancy diagnosis is shown in detail in Table 4. The most common cancers in female patients were hematologic malignancies (n:18, 27.7%) and breast cancer (n:16, 24.6%). In male patients, hematologic malignancies (n:42, 38.2%) and lung cancer (n:27, 27.5%) predominated. Of the 164 patients with available tissue diagnosis, 29.3% (n:48) had multiple myeloma, 22.6% (n:37) had squamous cell carcinoma, and 18.9% (n:31) had adenocarcinoma.

A total of 66 patients were diagnosed as drug-induced hypercalcemia. The criteria for drug-induced hypercalcemia was normalization of calcium levels after discontinuation of the drug. The list of the drugs that have been associated with hypercalcemia is presented in Table 5. The most frequent cause of drug-induced hypercalcemia was calcitriol. Additionally, 14 patients diagnosed with PHPT and two patients diagnosed with HCM continued to use thiazide diuretics, which may have also contributed to hypercalcemia.

Discussion

In our study, we identified 643 patients with persistent hypercalcemia over a 3-year period and 19.8% of them were not further investigated. The majority of these patients were asymptomatic and had mild to moderate hypercalcemia. This data indicates a high frequency of unexamined patients, particularly in the asymptomatic and non-severe hypercalcemia group. Therefore, physicians' awareness of this issue should be increased. In a study, it was observed that 72% of patients presenting to general practitioners and found to have hypercalcemia and 13% of patients presenting to hospitals were not further investigated (13). In another multicenter study including 9 hospitals and 13 outpatient clinics, 67% of patients with hypercalcemia did not undergo further evaluation (11). In another hospital-based study; 32,8% of patients with sustained hypercalcemia were unevaluated regarding hypercalcemia etiology (23).

Of patients in our study, examined for the etiology of hypercalcemia, 58.3% were asymptomatic who were incidentally diagnosed. Similarly, in another study in a hospital population, 64.5% of patients had no clinical suspicion for hypercalcemia (12). In symptomatic patients, the most common reason for hospital admission was neurological complaints and the most common symptom among these was fatigue and/or weakness. Several studies in the literature have reported varying results regarding symptoms. Gastrointestinal complaints were found most frequently in patients with hypercalcemia in some studies (24,25), while neurologic symptoms were found most frequently in two different studies that evaluated patients admitted to the emergency department (26,27). The frequency of being symptomatic increased significantly as the severity of hypercalcemia increased, which is consistent with the literature (2).

The most common cause of hypercalcemia in this study was PHPT followed by HCM. It is widely reported in the literature that PHPT and HCM account for approximately 90% of cases (1,6,7). Although these two causes constitute the majority of cases in our hospital, accounting for 69.8% of cases; this rate is lower compared to the literature. In our hospital, drug-related hypercalcemia was the third most common cause, occurring in 12.8% of cases, although it is less common in literature. Iatrogenic hypercalcemia was detected in 1.9-5.75% of patients in other studies (8,13,23,24). These data demonstrate the significance of closely monitoring drug side effects and carefully evaluating the medical treatment of patients with hypercalcemia.

Studies conducted in hospital populations have found malignancy to be the most common cause of hypercalcemia(12,24,25). However, in our study, PHPT was the most common diagnosis. But in hospitalized patients, HCM was the most common cause, which supports existing inpatient population data (8,28). PHPT was the leading diagnosis in outpatients and was found to be similar to outpatients in other studies (29,30).

In 11.2% of the patients, the diagnosis could not be determined. Among this group, PTH levels were not measured in 30 patients, some of whom were being followed up for malignancy and receiving bisphosphonate treatment. We included these patients in the undiagnosed group due to incomplete data.

Serum calcium levels are generally higher in HCM, lower values may suggest hyperparathyroidism (31). In a review article, mean calcium levels in different etiologies in different studies were evaluated and it was observed that the best discrimination level for patients with PHPT was

12.5mg/dl and below (7). In our study, the mean±SD of calcium in patients with PHPT was 11.8±0.8 mg/dl, while it was 13.6±1.7 mg/dl in patients with HCM.

Parathyroidectomy was performed in 50.3% of patients diagnosed with PHPT. In other studies, parathyroidectomy was performed in 18% (11) and 28% (32) of patients. The high rate in our study may be attributed to the referral of patients for surgery from different centers due to the location of our hospital, the surgical experience in parathyroidectomy, and the exclusion of patients with PHPT with a calcium level of 10.5-11mg/dL.

Of the 93 patients who underwent parathyroidectomy, adenoma was the most common parathyroid pathology, and these findings are consistent with previous studies (33,34). Three patients with MEN syndrome had multiple lesions (adenoma or hyperplasia), while three patients had a single adenoma. It is important to note that familial hyperparathyroidism may also be present in patients with a single adenoma.

Hematologic malignancies were the leading cause of HCM in both males and females. Among these, multiple myeloma was the most common diagnosis. Lung cancer was the second most common cause, followed by breast cancer. Some studies have reported that lung and breast cancer are the most frequent causes of HCM (13,35,36). In some other studies, multiple myeloma was found to be the most common cause of hypercalcemia as in our study (37,38). PTH level was not measured in approximately half of the patients diagnosed with HCM. Additionally patients with PTH level ≥50pg/ml were not evaluated for PHPT which may accompany malignancy. Concomitant malignancy was present in 10.3% of PHPT patients. Studies have shown that in patients with PHPT and malignancy, the frequency of the other one increases (39,40). In one study, PHPT was found in 15% of patients presenting with hypercalcemia and malignancy (41). Since malignancy and PHPT may coexist, and the initial objective of laboratory evaluation is to distinguish PTH mediated hypercalcemia from non-PTH-mediated hypercalcemia. Therefore, serum PTH should be measured once hypercalcemia is confirmed, even in patients with a known cancer diagnosis.

The study has several limitations. Firstly, due to its retrospective design the patients' data are incomplete. Additionally, there may have been patients who sought ongoing evaluation and treatment at other centers and did not return for follow-up at our institution. Data from other hospitals are not accessible through our hospital system. This contributes to the increase of missing data. Secondly, the lack of standardization due to the fact that the patients were evaluated by different physicians. Thirdly, mildly hypercalcemic and possibly asymptomatic patients with calcium levels <11mg/dl were excluded due to missing data. Finally, evaluations were made according to the presence of bone metastases and PTH levels in HCM because PTHrP level could not be measured in our hospital. The study's strengths are the inclusion of all patients who met the specified criteria within a 3-year period and conducted with a large patient population.

This study demonstrates that hypercalcemia is often underrecognized due to its asymptomatic nature, potentially leading to missed diagnoses. Our findings indicate that diagnostic tests may be inadequate, particularly in asymptomatic and/or mild-to-moderate cases. It is essential to evaluate clinical indicators and consider drug-induced hypercalcemia, which is notably prevalent in our study. For persistent hypercalcemia, initial measurement of parathyroid hormone (PTH) levels is crucial, even when malignancy is present. Recognizing the possibility of multiple concurrent causes, including malignancy, drug use, and primary hyperparathyroidism (PHPT), is vital for effective management. Further studies with larger cohorts are needed to better define the implications of mild hypercalcemia.

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