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# **RESEARCH ARTICLE**

## **PROFILE OF HYPERCALCEMIA IN HOSPITALIZED PATIENTS: A PROSPECTIVE STUDY**

Preet Mohinder S Sohal,<sup>1</sup> Dinesh Gupta,<sup>2</sup> Shveta Garg,<sup>3</sup> Jashan Sandhu,<sup>4</sup> J S Sandhu<sup>\* 5</sup>

<sup>1</sup>Assistant Professor, Department of Nephrology, DMC Ludhiana <sup>2</sup>Professor & Head, Department of Medicine, DMC Ludhiana

<sup>3</sup>Resident, Department of Medicine, DMC Ludhiana

<sup>4</sup>Senior Resident, Department of Pathology, PGI Chandigarh

<sup>5</sup>Professor & Head \*, Department of Nephrology, DMC Ludhiana

# Corresponding Author: Dr J S Sandhu, Professor and Head, Department of Nephrology, Dayanand Medical College, Ludhiana-141001, Punjab, Mobile: 9815542146

#### Abstract

**Background**: Prospective studies on the profile of hypercalcemia in hospital population are scanty. Our objective was to determine the causes, relative prevalence and outcome of hypercalcemia in our hospital. **Material and methods**: All patients admitted with hypercalcemia over two-year period were prospectively studied for clinical profile and outcome. **Results**: Fifty two patients had hypercalcemia. The mean age was  $56.6\pm14.2$  years with almost equal male to female ratio. The commonest etiological cause of hypercalcemia was malignancy related (44%), followed by hyperparathyroidism (13.4%), drug induced (9.6%), granulomatous diseases (9.6%) and acute pancreatitis and chronic renal failure (3.8%) each. In 8 (15.3%) patients, exact etiology could not be ascertained. The commonest clinical manifestations were gastrointestinal (34%) followed by neurological (29%), bony pains and fractures (21%), renal (13%) and vague generalised (15%). Mild, moderate and severe grades of hypercalcemia were observed in 25%, 44% and 30% respectively. The overall mortality was 25%. **Conclusion**: The major cause of hypercalcemia is malignancy in our North Indian patients. Primary hyperparathyroidism, granulomatous diseases and iatrogenic hypervitaminosis D are also significant. Hypercalcemia is an important medical emergency and if diagnosed and treated properly can save many lives.

Key words: calcium, hypercalcemia of malignancy, hyperparathyroidism, vitamin D

#### **INTRODUCTION**

Many different disorders can cause hypercalcemia. The most common categories among hospitalized patients are malignancy, primary hyperparathyroidism (PHP) and vitamin D-induced hypercalcemia. <sup>[1, 2]</sup> The less frequent causes include drug-induced conditions (thiazide diuretics, lithium etc.), tuberculosis, immobilization, and recovery phase of rhabdomyolysis. Identification of the underlying disease is important, since the subsequent management is different for the various causes of hypercalcemia. Most of the epidemiological data on hypercalcemia in hospitalized patients is retrospective. <sup>[3, 4]</sup> Our objective was to prospectively study the prevalence, etiology and outcome of hypercalcemia in hospitalized patients.



## MATERIAL AND METHODS:

The study was done in the department of medicine and its allied specialities in our tertiary care medical college hospital over a period of two years. The study was cleared by the Institutional Ethical Committee and approved by the State Medical University. All adult patients with hypercalcemia were included. Hypercalcemia was defined as serum calcium >10.5 mg/dL. Hypercalcemia was classified based on total serum levels <sup>[5]</sup> as follows:

- Mild: Total Calcium = 10.5 to 11.9 mg/dL
- Moderate: Total Calcium = 12 to 13.9 mg/dL
- Severe (Hypercalcemic crisis) = Total Calcium 14 to 16 mg/dL

The biochemical reports of clinical biochemistry department were screened daily. All adult patients with serum creatinine above 10.5 mg/dL were seen in the relevant departments. Pseudohypercalcemia was excluded by repeating serum calcium and the serum calcium was adjusted according to the serum albumin levels by using the formula.<sup>[6]</sup>

"Adjusted total calcium (mg/dL) = Total calcium (mg/dL) + 0.8 (4.0 - Albumin (g/dL)"

After taking an informed written consent, a detailed clinical history and complete examination was done in each patient and recorded in the Performa. All patients underwent routine investigations including hemogram, ESR, routine urine examination, blood sugar, blood urea, serum creatinine, serum electrolytes, serum calcium, serum phosphorus, liver function tests, total serum proteins, serum albumin, serum 25 (OH) vitamin D, ECG, ultrasound and X-rays of chest, skull and spine. Special tests were done depending upon the suspected clinical diagnosis namely parathyroid hormone and CT of parathyroid glands for suspected hyperparathyroidism; bone marrow examination and serum electrophoresis for multiple myeloma; serum angiotensin converting enzymes for Sarcoidosis; and relevant biopsy for a suspected malignancy or granulomatous disease. Patients were treated on the standard line of treatment. Morbid events and outcome were recorded in each case. Relevant statistical methods were applied. P<0.05 was considered as statistically significant.

## RESULTS

The prevalence of hypercalcemia was 52 cases (25 males and 27 females) out of the total 55018 adult medical admissions over two years, thus giving a prevalence of 0.095%. The main age of patients with hypercalcemia was  $56.6\pm14.2$  with range of 14 to 85 years. Half of the patients were from 5<sup>th</sup> and 6<sup>th</sup> decades and another  $1/3^{rd}$  from 7<sup>th</sup> and 8<sup>th</sup> decade. (Figure 1).

Malignancy was the commonest cause of hypercalcemia (44%) followed by

hyperparathyroidism, drug induced and granulomatous diseases. Solid organ malignancies included 2 cases each of breast cancer and carcinoma of oesophagus, metastatic deposits in spine in 2 cases and brain metastasis in one. Out of the iatrogenic hypercalcemia, four patients had received injudicious injections of Vitamin D with hypervitaminosis D and one was lithium induced in a bipolar disorder. (Table 1)

The clinical sypmtomatology is depicted in Figure 2. Gastrointestinal, neurological and skeletal symptoms were commonly observed. Renal failure was observed in 15% of patients with hypercalcemia.



Maximum number of patients had moderate hypercalcemia followed by severe and mild grades (Figure 3).

Overall mortality was 25%. Comparing the variables amongst survivors with non-survivors, the hospital stay, central nervous system and gastrointestinal involvement and mild and moderate hypercalcemia were found to be significant. (Table 2)



Figure1: Showing age distribution

Figure 2: Showing clinical sypmtomatology



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## Figure 3: Showing grades of hypercalcemia



#### **Table 1: Etiology of Hypercalcemia**

Causes	No of patients(n) Male		Females	Percentage
1)Hematological malignancy	16	7	9	30.7%
Multiple myeloma	9	4	5	17.3%
Lymphoma	7	3	4	13.4%
Leukemia	0	0	0	
2) Solid organ malignancy	7	2	5	13.4%
3)Hyperparathyroidism	7	2	5	13.4%
4)Drugs	5	1	4	9.6%
5)Granulomatous disorder				
a)Tuberculosis	3	3	0	5.7%
b)Sarcoidosis	2	2	0	3.8%
6)Idiopathic	8	5	3	15.3%
7)Miscellanous				
A) Acute pancreatitis	2	1	1	3.8%
B)Chronic kidney disease	2	2	0	3.8%



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Table 2: Comparison between survivors and non-survivors						
Variable	Survivors	Non survivors	Z Value	P Value		
Age mean ± SD	52.3±15.5	59.4±14.9	1.7	< 0.10		
Sex distribution	12:13	13:14	0.0001	>0.10		
			Chi-square			
Symtomatology	n(%)	n(%)				
GIT	7(28%)	7(26%)	0.17	>0.10		
CNS	5(20%)	5(18.5%)	0.14	>0.10		
Renal	3(12%)	0(0%)	1.85	< 0.10		
Musculoskeletal	1(4%)	2(7.4%)	0.53	>0.10		
General	6(24%)	3(11.11%)	1.23	>0.10		
GIT+CNS	0(0%)	6(22%)	2.51	<0.05*		
GIT+Musculosketal	0(0%)	1(3.7%)	0.97	>0.10		
GIT +Renal	0(0%)	1(3.7%)	0.97	>0.10		
GIT+General	1(4%)	1(3.7%)	0.06	>0.10		
Renal+CNS	1(4%)	0(0%)	0.06	>0.10		
Renal+General	0(0%)	1(3.7%)	0.97	>0.10		
CNS+Musculoskeletal	1(4%)	0(0%)	1.05	>0.10		
Calcium level at admission	14.44±1.61	14.31±3.07	0.19	>0.10		
Etiology of hypercalcemia						
-Multiple Myeloma	5(20%)	4(14.8%)	0.49	>0.10		
-Lymphoma	4(16%)	3(11.11%)	0.52	>0.10		
-Solid organ malignancy	3(12%)	4(14.8%)	0.30	>0.10		
-Hyperparathyroidism	3(12%)	5(18.5%)	0.65	>0.10		
-Drug induced	1(4%)	3(11.11%)	0.53	>0.10		
-Granulomatous diseases						
A )Tuberculosis	2(8%)	1(3.7%)	0.66	>0.10		
B)Sarcoidosis	2(8%)	0	1.5	>0.10		
-Idiopathic	4(16%)	3(11.11%)	0.52	>0.10		
-Acute pancreatitis	0	2(7.4%)	1.39	>0.10		
-Chronic Kidney Disease	1(4%)	1(3.7%)	0.06	>0.10		
2						
Severity of hypercalcemia						
Mild	3(12%)	11(40%)		<0.05*		
Moderate	16(64%)	8(30%)		<0.05*		
Severe	6(24%)	8(30%)		>0.10		
Length of hospital stay	11.56+/-3.69	8.52+/-5.06		<0.05*		

\*statistically significant, GIT-gastrointestinal, CNS-central nervous system

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#### DISCUSSION

Hypercalcemia was infrequent among hospitalized patients. The major cause (44%) of hypercalcemia was found to be malignancy. The relative prevalence of malignancy-related hypercalcemia seemed to reflect the relative prevalence of malignancy in the local population. Hematologic diseases, especially multiple myeloma and lymphoma were the most frequent type among malignancy-related hypercalcemia. With an unusually high association of hypercalcemia, about 40% of patients with lymphoma are known to eventually develop hypercalcemia. <sup>[7, 8]</sup> Extensive osteolytic bone destruction is seen in all patients with myeloma, hypercalcemia occurs only in 15% to 20%. The degree of hypercalcemia and bone lesions is not well correlated.<sup>[9]</sup> Breast carcinoma was relatively uncommon in our series as well as in other Asian studies <sup>[10, 11]</sup> in contrast to Western series with this carcinoma typically accounting for more than 20%. <sup>[12, 13]</sup> Primary hyperparathyroidism was the 2<sup>nd</sup> frequent cause of hypercalcemia, observed in 13% in our study. Similar observations have reported from other Asian countries, 15% from Japan<sup>[11]</sup> and 5.5% from Hong Kong.<sup>[10]</sup> A single enlarged parathyroid gland (adenoma) is the cause in more than 85% of cases. Parathyroid carcinoma, not seen in any of our patients, probably accounts for less than 1% of cases of primary hyperparathyroidism. <sup>[14]</sup> Primary hyperparathyroidism is known to be the most common etiology for hypercalcemia in the outpatient setting.<sup>[15,16]</sup> Mundy et al reported that primary hyperparathyroidism was diagnosed in 111 patients (54%) in 207 hypercalcemic patients in an urban area of 1 million people over a period of 5 months in the USA.<sup>[15]</sup>

We detected five (Sarcoidosis in 3, Tuberculosis in 2) cases of granulomatous diseases. Hypercalcemia has been best studied in Sarcoidosis, is caused by inappropriate extrarenal production of 1, 25 (OH)  $_2$  D by activated macrophages with increased 1alpha-hydroxylase activity. <sup>[17, 18]</sup>

The mortality in our study was 25%. Underlying disease especially malignancy is the usual cause of mortality. Patients with both GIT and CNS symptoms were the poor prognostic factors as was the mild and moderate degree of hypercalcemia. Improved outcomes can be attributed to modern diagnostic capabilities leading to earlier diagnosis, along with the recognition that primary hyperparathyroidism common etiology for Hypercalcemic crisis.<sup>[19]</sup>

In **conclusion**, hypercalcemia is rare in hospitalized patients. Hypercalcemia is commonly observed in elderly patients. More than 80% of patients are in 5<sup>th</sup> to 8<sup>th</sup> decades of life. Malignancy and primary hyperparathyroidism are the two major causes of hypercalcemia. Drugs, particularly parenteral administration of Vitamin D, are emerging as an important preventable cause.

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