Original Article

Clinical and Etiological profile of Hypercalcemia in patients attending tertiary care Hospital in North India" An Observational Study

Manzoor Ahmad, Mubarak Naqash, Abdul Ahad Wani, Ishrat Majeed, Syed Tanzeela,

Abstract

Background:Hypercalcemia is a common medical condition in the setting of primary care, as well as emergency departments and patients admitted to hospital characterized by increased levels of serum calcium (>10.5 mg/dL), due to various underlying etiologies. Hypercalcemia presents a significant clinical challenge due to its diverse clinical presentations and potential for serious complications. Understanding clinical and etiological causes of Hypercalcemia is essential for accurate diagnosis, appropriate management, and improved patient outcomes. : In this study, we aimed to do a comprehensive profiling of patients presenting with persistent hypercalcemia to our hospital, encompassing its demographic characteristics clinical presentation, and diagnostic approach to determine the various underlying causative etiologies of hypercalcemia

Materials and methods: A cross sectional observational study was done involving 165 patients who were found to have hypercalcemia. After taking informed consent, relevant history was taken and detailed clinical examination was performed. All the patients were subjected to relevant investigations to identify the underlying etiology. The data was analyzed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 20.0., IBM Corp., Armonk, NY, USA).

Results: Our study included 165 patients reporting to the department of general medicine over 18 months period. The mean age of our patients was 65.20 ± 15.6 years .In our study we had 92 (55.75 %) male patients and 73 (44.25 %) female patients. Majority of our patients were asymptomatic. Gastrointestinal symptoms like pain abdomen and constipation were the most common presentation seen in 57 (34.5 %) and 54 (32.72 %) patients. Osmotic symptoms were seen in 30 (18.18 %) patients. Musculoskeletal complaints were present in18 (10 .90 %) patients. The most common causes was primary hyperparathyroidism (PHPT) in 90 (54.54%) followed by malignancy in 33 patients (20 %). Interestingly, we found emergence of unusual cause of hypercalcemia, namely vitamin D toxicosis (n = 12) in the non-parathyroid group of hypercalcemia.

Conclusion: In conclusion, the profiling of hypercalcemia is a multidimensional endeavor that necessitates a comprehensive understanding of its underlying mechanisms, diverse clinical presentations, and diagnostic intricacies. This study intends to serve as a valuable resource for healthcare professionals, offering insights into the complex terrain of hypercalcemia.

JK-Practitioner2024;29(2-3):21-24

Introduction

Hypercalcemia is defined as calcium concentration higher than 10.5 mg/dL. It is classified into mild, moderate, and severe, depending on

Author Affiliations

Manzoor Ahmad, Assistant Professor, **Mubarak Naqash,** Prof and Head, **Abdul Ahad Wani,** Assistant Professor, Department of General Medicine Skims Medical College Bemina Srinagar, **Ishrat Majeed,** Medical Officer, GMC Srinagar, **Syed Tanzeela**, Medical Officer, Department of General Medicine Skims Medical College Bemina Srinagar

Correspondence

Dr Abdul Ahad Wani, Assistant Professor, Department of General Medicine, Skims Medical College Bemina Srinagar
E.Mail: hajiahadwani@gmail.com
Mobile: +91-9596542669

Indexed

EMBASE ,SCOPUS ,IndMED ,ESBCO,Google Scholar ,besides other National and International Databases.

Cite this article as: Ahmad M, Wani AA, Majeed I, Tanzeela S, Naqash M. Clinical and Etiological profile of Hypercalcemia in patients attending tertiary care Hospital in North India" An Observational Study JK Pract2024;29(2-3):21-24

Full length article available at **jkpractitioner.com** one month after publication

Keywords

Hypercalcemia, Hyperparathyroidism, Multiple Myeloma, Vitamin D Intoxication

calcium values: mild 10.5–12 mg/dL, moderate 12.1–14 mg/dL, and severe >14 mg/dL [1, 4,]

Hypercalcemia is a common finding in the setting of primary care, as well as emergency departments and patients admitted to hospital [2, 3, 5]. Primary hyperparathyroidism and malignancy are the most common, accounting for greater than 90 percent of cases [6]. Hypercalcemia in otherwise healthy outpatients is usually due to primary hyperparathyroidism while malignancy is more often responsible for hypercalcemia in hospitalized patients. Malignancies like squamous cell carcinoma, urinary tract cancers (renal cell and bladder carcinoma), breast cancer, multiple myeloma, non-Hodgkin's lymphoma, etc., can lead to hypercalcemia[7,10].Primary hyper parathyroid ismresultsmostoften(75-80%)fromoccurrence of one or more adenomas in previously normal parathyroid glands, although in 20 % of cases diffusehyperplasiaofallparathyroidglandsmaybepresentor,rarely,parathyroidcarcinoma may be found (1-2 %)[8,9]Other causes of hypercalcemia include granulomatous disease like sarcoidosisandtuberculosis[10].Endocrinopathiesliket hyrotoxicosis,phaeochromocytomaand adrenal insufficiency can cause hypercalcemia[11,12,13]. Prolonged immobilization is an important factor to consider in patients with prolonged immobility[14].Medications like Lithium, thiazide diuretics, teriparatide Vitamin D and calcium supplementation can cause hypercalcemia [15, 16]

Patients with mild hypercalcemia (Sr calcium < 12 mg/dL) may be asymptomatic or may report nonspecific symptoms like constipation fatigue and depression and are often detected on routine laboratory evaluation for other reasons. Symptoms of hpercalcemia especially with an acute rise include neurological, muscular, gastrointestinal, renal, and cardiovascular systems. Neuropsychiatric symptoms include confusion, somnolence, anxiety, cognitivedeficits, behavior changes and even coma in patients with severe hypercalcemia. Gastrointestinal symptoms encompass nausea, vomiting, anorexia, constipation, abdominal pain, rarely pancreatitis, and peptic ulcer disease [17]. Renal manifestations include nephrolithiasis, distal renal tubular acidosis, nephrogenic diabetes insipidus, and even renal failure in untreated cases [18]. Cardiac manifestations include bradycardia, heart block, and other arrhythmias, which can be life- threatening and shortened QT intervals, prolonged PR intervals, and widened QRS complex on ECG [19].

Physical examination in a patient with hypercalcemia may be completely normal but may sometimes show alterations in their heart rate or rhythm detectable on palpation of the pulse or cardiac auscultation. Patients can also have diminished deep tendon reflexes. A musculoskeletal exam may reveal reduced muscle tone.

History and physical exam, including reviewing all medications, are crucial to help determine the etiology of hypercalcemia. A key diagnostic step is checking a PTH level to clarify if hypercalcemiais PTH-mediated or not. If PTH levels are within normal limits or elevated, this is considered PTH-mediated hypercalcemia. The next step would be to check a 24-hour urinary calcium test to differentiate between hyperparathyroidism (associated with high urinary calcium levels) and Familial Hypocalciuric Hypercalcemia (associated with low urinary calcium levels).If PTH levels are suppressed, then PTH-independent etiologies of hypercalcemia should be considered. Additional laboratory investigations to aid in the diagnosis of non-PTH mediated hypercalcemia may include ionized calcium, phosphorus, magnesium,alkaline phosphatase,KFT 25-dihydroxy vitamin D, PTHrP, serum and urine electrophoresis, thyroid panel, serum metanephrines, Sr ACE levels IGF-1 besides tissue biopsies based on highest probability causes [20].

Materials and Methods:

This observational prospective study was conducted in the Department of General Medicine SKIMS MedicalcollegeSrinagaroveraperiodof1yearonadults> 18yearofagediagnosedas

having hypercalcemia (corrected Sr calcium > 10.5 mg/dl0 on two separate occasions. A total of 180 patients reporting to department of Medicine SKIMS Medical college hospital fulfilling the inclusion criteria were included in the study. After taking informed consent, relevant history was taken and complete examination was done. All the patients were subjected to baseline investigations like complete blood count with erythrocyte sedimentation rate , Kidney function test, Liver function test, Serum sodium, Sr potassium and thyroid function test besides Chest Radiograph.

SerumVitamin D levels ,serum iPTH levels and 24 hour urinary calcium levels were checked.

Serum electrophoresis, urine electrophoresis, USG neck/abdomen, CT neck/chest/abdomen, skeletal survey, Technetium Sestamibiscan, bonescans, BMD and bone marrow biopsy was done wherever it was considered relevant.

The collected data was entered into a Microsoft Excel Spreadsheet. Categorical values were summarized in the form of frequency and percentage while continuous variables were summarized in mean and standard deviations. The data was analyzed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 20.0., IBM Corp., Armonk, NY, USA).

Results: Our study included 165 patients reporting to the department of general medicine over 18 months period. The patients were aged18-73, with18.3% aged18-40, 40.2% aged 41-60 and 41.4% aged more than 60 years. The mean age of our patients was 65.20±15.6 years. In our study we had 92 (55.75 %) male patients and 73 (44.25 %) female patients as depicted in Table 1.

Table1:Age&Gender Distribution		
Agein Years(Mean+-SD)	65.20±15.6	
GenderN(%)	Males	92 (55.75%)
	Females	73 (44.25%)

Table1depicts the mean age and gender distributionof our study group of patients (n=165)

96 out of 165 patients (58.18%) had PTH depend enthypercalcemia. Mean age in this group was 64.32 ± 13.15 years. Mean serum calcium was 13.24 ± 1.65 mg /dl. and mean serum phosphorus was 3.20±1.46mg/dl.78 out of these 96 patients (81.25%) were females and18(18.75%) were males. The mean age of females was 62.4 ± 12.40 years while that of males was 54.52 ±12.60 years. Mean serum calcium levels were 12.98 mg/dl and 13.70 mg/dl in males and females respectively. Ultrasound neck diagnosed an adenoma in 72 (75 %) patients while sestamibi scan was positive in 86 (89.58 %) of our patients.

In the remaining 69 patients who had PTH independent hypercalcemia the mean age was64.65 ± 13.42 years with a mean serum calcium of 13.16±1.68mg/dl and a mean serum phosphorus level of 4.0±1.98mg/dl. Forty one patients (59.4%) were males and 28 (40.5%) were females. Inmale group the mean age was 62.23±11.34 years and the mean calcium was13.65±2.42mg/dl. Among females mean age was 63.24 ± 12.22 years and the mean calcium was 12.67 ± 1.56 mg/dl.

Majority of our patients were asymptomatic. Gastrointestinal symptoms like pain abdomen and constipation were the most common presentation seen in 57 (34.5 %) and 54 (32.72 %) patients.

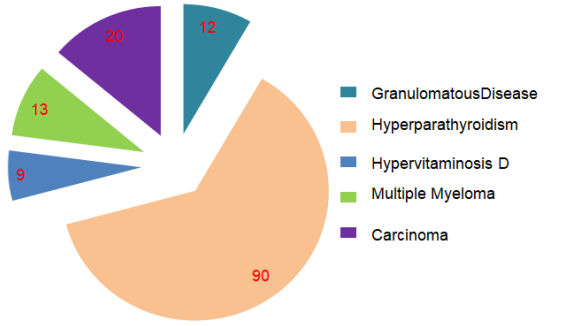
Table2:ClinicalParametersofhypercalcemicPatients		
ClinicalParameter		
AbdominalPain		57 (34.5 %)
Constipation		54 (32.72 %)
OsmoticSymptoms		30 (18.18 %)
Musculoskeletalcomplaints Bone Pains		18 (10.90 %)
Encephalopathy		14 (8.48%)
Otherclinical Features	**Breathlessness**	10 (6.06 %)
	Oliguria	9 (5.45%)
	Cough	8 (4.84%)
	Weakness lowerlimbs	6 (3.63 %)
	Haemoptysis	4(2.42%)
	GTCS	2 (1.2 %)

Osmotic symptoms were seen in 30 (18.18%) patients. Musculoskeletal complaints were present in18 (10 .90 %) patients as depicted in Table 2. Fourteen patients (8.48 %) had encephalopathy. Forty four (26.6 %)of our patients had nephrolithiasis The most common cause of hypercalcemia in our study PHPT which was seen in 90 (54.54 %) patients followed by malignancy (solid organ malignancy in 20 (12.12 %) patients and multiple myeloma in 13 (7.87 %). The third frequent cause of hypercalcemia in our study was Vitamin D intoxication and 12 (7.2 %) of our patients had higher than normal levels of Vitamin D. Other etiologies in decreasing order of frequency were Chronic kidney disease (n = 6 , 3.63 %) , Sarcoidosis (n= 5 ,3.03%) , tuberculosis (n= 4 , 2.42 %) , Chronic liver disease (n= 3,1.81 %) Despite detailed investigations the etiology of hypercalcemia could not be as curtained in 12(7.2%) patients.

The most common cause of PTH-dependent hypercalcemia was PHPT. Except for one patient with multiple endocrine neoplasia all patients with PHPT had a solitary parathyroid adenoma. most common site of the culprit parathyroid adenoma was left inferior parathyroid adenoma (48.9%), followed by right inferior parathyroid adenoma (RIPA)(40.8%), left superior parathyroid adenoma (7.2%), and right superior parathyroid adenoma (3.1%).

The most common malignancy causing hypercalcemia was multiplemyeloma, contributing to13 cases, followed by squamous cell carcinoma of the lung (8cases).Others in decreasing order were acute leukemia, lymphoma, chronic lymphoproliferative disorder, unknown primary with metastasis, adenocarcinoma lung, carcinoma gall bladder, carcinoma breast with metastasis, hepatocellular carcinoma. Twelve patients with hypercalcemia had Vitamin D intoxication.

Etiologic profile of hypercalcemia (n=165)



Discussion:

The current study was carried out at SKIMS Medical College and Hospital, Srinagar over a period of 16 months i.e., 1st January 2023to 1st June 2024. Consecutive patients with confirmed hypercalcemia on two occasions were enrolled in our study. The mean age of the cohort was 65.20 years ±15.6 years (range 18 to 95 years), which was higher than the study conducted by Kuchay et al. (55.2 years ±17 .9) [21]. In our study we had 92 (55.75 %) male patients and 73 (44.25 %) female patients. This was in conformity to the observations by Kuchay et al. who studied 552 patients with hypercalcemia and reported male preponderance(332 males and 230 females)[21]

In this prospective observational study, we found that

the most common cause of hypercalcemia was PHPT (48.4%) followed by malignancy (26.06%)VitaminDintoxicationwas responsible for hypercalcemia in7.2 % patients.

Hypercalcemia is a common electrolyte abnormality, which, if left undiagnosed, can lead to significant morbidity and mortality. Early detection and correction of hypercalcemia are of paramount importance. Hypercalcemia is a marker of an underlying pathology ranging from a serious entity like malignancy to a benign entity like familial hypocalciuric hypercalcemia. Thus, hypercalcemia always warrants a thorough search for an underlying disease entity and usually treatment of the underlying etiology leads to the correction of hypercalcemia.

The etiology of hypercalcemia differs according to the clinical setting. The most common cause of hypercalcemia in our patients is PHPT making it the third most common endocrine disorder after diabetes mellitus and thyroid disorders. On theother hand in hospitalized patients, malignancy is the most common cause of hypercalcemia.

A retrospective study was done to determine the profile of hypercalcemia in all patients who presented to a tertiary care hospital in North India. A total of 255830 patients presented to the hospital from January1, 2014, to June 30, 2015 (18months). Among them, calcium measurement was done in 26297 (10.2%) patients. A total of 552 patients were found to have hypercalcemia. Of these 552 patients, 15 (2.7%) patients had transient hypercalcemia while 537 (97.3%) had sustained hypercalcemia. The incidence of hypercalcemia was 2.09%, being transient at 0.05% and sustained at 2.04%. The most common cause in the sustained group was malignancy (23.1%), followed by PHPT (21.9%). Most cases of PHPT were asymptomatic. A significant number of patients had hypercalcemia of advanced CLD (n = 34) and Vitamin D intoxication (n = 21). Nevertheless, the study did have certain lacunae. The study had a retrospective design; besides, being a cross-sectional study, follow-up data, and clinical outcomes were not available.[21]

In our study most common cause of hypercalcemia was PHPT.PHPT was previously diagnosed once the disease was symptomatic but with the widespread availability of auto analyzers, early detection of PHPT at an asymptomatic stage is becoming more common in India. In the present study, most of the patients with PHPT had asymptomatic disease.

Malignancy was second commonest cause of hypercalcemia in our study which was different from study done by Gupta et al [22]

Vitamin D intoxication which is now a day's becoming one of the important causes of hypercalcemia due to unregulated use of VitaminD especially parentally was the third frequent cause of hypercalcemia in our study. Various studies conducted in India have demonstrated the rising trend of Vitamin D intoxication in the masses, [23]. Thus, irrational routine use of Vitamin D supplements, especially bolus parenteral preparations, should be discouraged.

Conclusion:

The most common etiology was PHPT followed by malignancy.

This study had some limitations: Being a single-center study extrapolation of these results on other populations needs to be confirmed.

References:

1. Basso SMM,LumachiF,NascimbenF,etal.Treatment of acute hypercalcemia.MedChem 2012;8(4):564-68
2. Dalemos,EggerstenR,herpeP,etal. Longterm follow-up of patients with elevated serum calcium concentrations in Swedish primary care;Scand JPrimHealthCare 2012;30:48-54
3. LinderG, FelberR,SchwarzC,et alHypercalcemiainEd; prevalence,etiology, and out come ;AmJEmerg Med2013;31657-60
4. Chang WTW, RadinB, McCurdy MT.Calcium, magnesium, andphosphate abnormalities in the emergency department. Emerg Med Clin North Am. 2014;32(2):349-66.
5. Catalano A, Chila D, Bellone F , et al Incidence of hypocalcemia and hypercalcemia in hospitalized patients : Is it changing ? j Clin Transl Endocrinology 2018 ;13:9-13.
6. Lafferty FWDifferential diagnosis of hypercalcemia. J Bone Miner Res. 1991;6 Suppl 2:S51.
7. Asonitis N , Angelousi A , Zafeiris C,_ HYPERLINK "https://orcid.org/0000-0001-8389- 1360"LambrouGI, Dontas I, Kassi E.. Hypercalcemia of Malignancy … HormMetab Res 2019; 51: 770–778.
8. Weber CJ, Sewell CW, Mc GarityWc. Persistent and recurrent spopradic primary hyperparathyroidism :histopathology, complications and results of reoperation, surgery 1994 ; 116 (6):991-998.
9. ShaneE,BilezikianJP.Parathyroidcarcinoma:arev iewof62patientsEndocrRev1982;3: 218-226.
10. Guise TA, Wysolmerski JJ. Cancer-Associated Hypercalcemia.N Engl J Med.2022 Apr 14;386(15):1443-1451.
11. Burman KD, Monchik JM, Earll JM, Wartofsky L. Ionized and total serum calcium and parathyroid hormone in hyperthyroidism. Ann Intern Med. 1976 Jun;84(6):668-71.
12. MuneT,KatakamiH,KatoY,YasudaK,Matsukura S,MiuraK.Productionandsecretionof parathyroid hormone-related protein in pheochromocytoma: participation of an alpha- adrenergic mechanism. J Clin Endocrinol Metab. 1993 Mar;76(3):757-62
13. De Silva SDN, Aravinthan M, Katulanda P. Glucocorticoid-induced adrenal insufficiency:

anuncommoncauseofhypercalcaemia.EndocrinolDiabetesMetabCaseRep.2022May 01;2022
14. Cano-Torres EA, González-Cantú A, Hinojosa-Garza G, Castilleja-Leal F. Immobilization induced hypercalcemia. Clin Cases Miner Bone Metab. 2016 Jan-Apr;13(1):46-7
15. McHenry CR, Lee K. Lithium therapy and disorders of the parathyroid glands. EndocrPract. 1996 Mar-Apr;2(2):103-9.
16. Wermers RA , Kearns AE, Jenkins GD, et al Incidence and clinical spectrum of thiazide induced-associated hypercalcemia..Am J Med 2007;120:911.e 9-15.
17. Inzucchi SE. Understanding hypercalcemia. Its metabolic basis, signs, and symptoms. Postgrad Med 2004; 115: 69–70 73–66
18. AuronA,AlonUS:Hypercalcemia:aconsultant'sapproach.PediatrNephrol.2018, 33:1475-1488. 10.1007/s00467-017-3788-z
19. ThillainadesanS,TwiggSM,PereraN.Prevalence, causesandassociatedmortalityof hypercalcaemia in modern hospital care. Intern Med J. 2021; imj.15402.
20. MotlaghzadehY,BilezikianJP,SellmeyerDE:Rare causesofhypercalcemia:2021update. J Clin Endocrinol Metab. 2021, 106:3113-3128. 10.1210/clinem/dgab504
21. Kuchay MS,Kaur P,Mishra SK,Mithal A.Thechangingprofileof hypercalcemiainatertiarycares ettinginNorthIndia: An18-month retrospective study. Clinases Miner Bone Metab 2017;14:131-5.
22. GuptaCM:Evaluationandaetiopathogenesisofhypercalcaemia.Astudyof89patients.J AssocPhysIndia.1990,38:337-339.
23. Raizada N, Goyal A, Singla R, Sreenivas V, Gupta N, Khadgawat R. Changing trend in vitamin D status from2008 to2016: An experience from a tertiary care institute in North India.IndianJEndocrinol Metab2020;24:150-4.