ORIGINAL ARTICLE OPEN ACCESS

The Impact of Metastatic Bone Cancers on Serum Calcium Levels: A Focused Analysis of Patient Outcomes

Muhammad Khizar Memon[1], Syed Uzair Mahmood[2], Sidra Memon[3], Azhar Rashid[4], Muhammad Ali Memon[5], Shahzad Ali Jiskani[6]

[1]Postgraduate Trainee, Allegheny Health Network, United States, [2]Consulant Epidemiologist, SHINE Humanity, Karachi, Sindh, Pakistan, [3]Resident Physician, Piedmont Macon Medical Center, Georgia, [4]Consultant Oncologist, NCCI, Karachi, Sindh, Pakistan, [5]Consultant Oncologist and HOD, Department of Oncology, Indus Medical College, Tando Muhammad Khan, Sindh, Pakistan, [6]Department of Pathology, Chandka Medical College, SMBBMU, Larkana, Sindh

ABSTRACT

Background: Metastatic bone cancers are a significant clinical problem because metastasis disrupts normal bone homeostasis, including calcium dysregulation. Much less is known about hypocalcemia and its clinical consequences. The study analyzed serum calcium changes in metastatic bone cancer patients, assessed differences across diagnoses and clinical stages, and evaluated alkaline phosphatase levels and types of bone lesions.

Methods: A prospective study was conducted on 100 metastatic bone cancers using convenience sampling, at Indus Medical College Hospital, between March and April 2020. The patients were categorized based on the principle tumor type, clinical stage, and bone scan results. Serum calcium, corrected calcium, albumin, and ALP are measured and analyzed using descriptive and inferential statistics. Data analysis was done by SPSS using one-way ANOVA, t-tests, Pearson correlation, regression analysis, and Chi-square tests. A p-value of <0.05 was considered significant.

Results: The mean serum calcium was 8.5 ± 0.6 mg/dl. The corrected calcium level of the patients with breast cancer was statistically lower compared with the prostate cancer patients - 8.3 ± 0.5 mg/dl (p = 0.01) compared with 9.0 ± 0.6 mg/dl. The levels of ALP in blastic lesions were higher than in lytic ones, amounting to 600 ± 300 IU/L and 250 ± 100 IU/L, respectively. There was marked regression in the main diagnosis and ALP levels, which occurred with serum calcium being altered in breast cancer.

Conclusion: Serum calcium levels vary significantly among different types of cancers and stages, suggesting a vigilant monitoring of calcium and ALP levels in clinical practice.

Keywords: Metastatic Bone Cancer, Serum Calcium, Alkaline Phosphatase, Calcium Dysregulation, Hypocalcemia

Corresponding Author:
Dr. Muhammad Khizar Memon,
Postgraduate Trainee
Allegheny Health Network, United States
Email: khizarali8@gmail.com
Doi: https://doi.org/10.36283/ziun-pjmd14-1/002

How to cite: Memon MK, Mahmood SU, Memon S, Rashid A, Memon MA, Jiskani SA The Impact of Metastatic Bone Cancers on Serum Calcium Levels: A Focused Analysis of Patient Outcomes. Pak J Med Dent. 2025 Jan;14(1): 3-9. Doi: https://doi.org/10.36283/ziun-pjmd14-1/002

Received: Mon, October 21, 2024 **Accepted:** Tue, December 10, 2024 **Published:** Fri, January 10, 2025

INTRODUCTION

Metastatic bone cancers represents a significant clinical challenge, particularly in its ability to disrupt normal bone homeostasis. Bone is a common site for metastasis, particularly from primary tumors of the breast, prostate, lung, and kidney[1,2]. The process of bone metastasis involved the complex interaction of tumor cells with the bone microenvironment, leading to either osteolytic or osteoblastic lesions, depending on the type of cancer and its biological behavior. These interactions frequently results in the dysregulation of bone remodeling processes, leading to abnormal serum calcium levels – a condition with significant clinical implications[3].

Calcium homeostasis is tightly regulated by the coordinated actions of the parathyroid hormone (PTH), calcitonin, and vitamin D, which act on the bones, kidneys, and gastrointestinal tract to maintain serum calcium levels with a narrow physiological range[4,5]. In the context of bone metastasis, however, this regulation can become profoundly disturbed. Tumor-induced bone resorption, driven by osteoclast activation, is a major cause of hypercalcemia in patients with metastatic bone disease. The release of calcium from the bone into the bloodstream not only leads to hypercalcemia but also contributes to a range of symptoms including nausea, vomiting, fatigue, and confusion, and in severe cases, can lead to renal failure and cardiac arrhythmias[6,7,8].

Conversely, certain metastatic cancers can induce hypocalcemia, though this is less common[9,10,11,12,13]. Hypocalcemia in the context of cancer may result from several mechanisms, including the consumption of calcium by rapidly growing tumor cells, or impaired calcium mobilization due to extensive osteoblastic activity, particularly in prostate cancer metastases[14]. The prevalence and severity of calcium dysregulation in metastatic bone cancer are underexplored, especially compared to primary bone cancers. Current literature reveals a gap in studies examining serum changes across different bone malignancies. While hypercalcemia is more common in metastatic disease, the mechanisms behind these differences are not fully understood, and clinical management remains challenging, with treatments offering only temporary relief. This study aimed to explore the changes in serum calcium levels in patients with metastatic bone cancers, providing a comparative analysis with patients suffering from primary bone cancers and a healthy control group. By examining these differences, we seek to enhance the understanding of the pathophysiological mechanisms underlying serum alterations in metastatic bone disease, and to inform clinical practice in the management of these patients. The findings could have significant implications for the clinical management of patients, potentially leading to improved prognostic tools and more effective therapeutic strategies. In addition to filling a critical gap in the literature, this study also challenges the prevailing assumptions about the uniformity of calcium homeostasis in bone-related malignancies.

METHODS

This was a prospective study conducted on patients diagnosed with metastatic bone cancers (No. IMC/ERB/2020-13). Data was collected at Indus Medical College Hospital, from March 2020 to April 2020. All 100 patients included using convenience sampling in the study had confirmed bone metastasis secondary to various cancers. The sample size was calculated using WHO sample size calculator with 95% confidence and 5% margin of error. The study includes patients with confirmed bone metastases through clinical diagnosis and imaging (bone scans). Serum calcium and albumin levels were documented. Patients with incomplete data or unconfirmed diagnoses were excluded. Clinical and laboratory variables were assessed, alongside cancer stages categorized as localized, advanced, or metastatic

Data analysis involved descriptive and inferential statistics. Continuous variables were summarized as mean ± SD, and categorical variables as frequencies. Comparative analysis used one-way ANOVA for serum calcium across cancer types, t-tests for calcium differences and lesion types, and Pearson correlation for relationship between calcium levels. Regression analysis identified predictors of calcium levels, including cancer types and ALP. Chi-square tests assessed hypo- and hypercalcemia rates across cancer types and stages. A p—value of <0.05 was considered as statistically significant.

RESULTS

Table 1: Demographic and Clinical Parameters of Patients (n=100)

Parameter	Mean ± SD	Median	Range
Age (in years)	58 ± 12	60	14-85
Serum calcium (mg/dL)	8.5 ± 0.6	8.5	7.3-9.7

Corrected calcium (mg/dL)	8.6 ± 0.7	8.6	7.4-9.8
Alkaline phosphatase (IU/L)	400 ± 300	300	100-700

The study took part with a total of 100 patients diagnosed with metastatic bone cancers. The mean age of the patients was 58 ± 12 years, ranging from 14 to 85 years (Table 1).

Table 2: Frequency Distribution of Primary Tumor Diagnosis (n=100)

Primary Tumor Site	Frequency	%
Breast	49	49%
Lung	11	11%
Prostate	9	9%
Testis	4	4%
Urinary bladder	4	4%
Bone	2	2%
Lymph node	2	2%
Nasopharynx	2	2%
Unknown	2	2%
Ovary	2	2%
Soft tissue	2	2%
Others	11	11%

The most common primary cancers were found to be breast cancer 49%, followed by 11% lung, 9% prostate etc., (Table 2).

The mean serum calcium level was at 8.5 ± 0.6 mg/dl, and 15% of the patients were classified as hypocalcemia, while 10% were hypercalcemic. The lowest average calcium levels were found in breast cancer patients at 8.3 ± 0.5 mg/dl, while the prostate cancer patients had the highest average of 9.0 ± 0.6 mg/dl. Mean corrected values for calcium levels were 8.6 ± 0.7 mg/dl. The overall prevalence of hypocalcemia was reduced after hypoalbuminemia has been corrected. A total of 10% of the patients still received the diagnosis of hypocalcemia. The corrected levels of calcium were compared between breast and prostate cancer patients to show that they were significantly lower in patients with breast cancer than in those with prostate cancer, with a value of $p < 0.05$.

Table 3: Comparison of Serum Alkaline Phosphatase and Corrected Calcium Levels with Type of Lesion (n=100)

Variable	Categories (Mean ± SD)		p-value
	Blastic lesion	***Lytic lesions***	
Alkaline phosphatase (IU/L)	600 ± 300	250 ± 100	<0.001
Serum calcium (mg/dL)	9.0 ± 0.6	8.3 ± 0.5	0.02

Independent t-test

The mean alkaline phosphatase level was 400 ± 300 IU/L. ALP levels were higher in blastic lesions compared with lytic lesions (mean: 600 IU/L for blastic and 250 IU/L for lytic) (Table 3).

Table 4: Relationship between Clinical Stage and Corrected Calcium Levels (n=100)

Clinical Stage	Corrected Calcium (mg/dL, mean)	p-value
Early Stage	9..1 ± 0.5	0.003
Locally Advanced	8.8 ± 0.4	
Metastatic Stage	8.3 ± 0.6	

Pairwise comparison conducted using ANOVA

Statistical analysis for serum calcium found the differences to be significant among primary diagnoses, p=0.03. The calcium levels differed at very significant levels among blastic, lytic and mixed bone lesions as estimated by p = 0.02; the blastic lesions showed a significantly higher level of serum calcium. Relationship of clinical stage with corrected calcium levels is summarized in (Table 4).

Table 5: Post-hoc Analysis for Clinical Stages of Tumors (n=100)

Comparison	Mean Difference	95% CI (Lower, Upper)	p-value
Early Vs. Locally Advanced	0.3	(0.1, 0.5)	0.02
Early Vs. Metastatic	0.8	(0.6, 1.0)	<0.001
Locally advanced Vs. Metastatic	0.5	(0.3, 0.7)	<0.001

Pairwise comparisons conducted using post-hoc analysis

Table 5 illustrates the corrected calcium levels across different clinical stages. A significant difference was observed between groups by post-hoc analysis.

Table 6: Linear Regression Analysis of Serum Calcium Levels (n=100)

Predictor Parameter	Coefficient	Standard Error	95% Confidence Interval	p-value
Primary Diagnosis (breast)	-0.60	0.20	-1.0-0.2	0.02
Primary Diagnosis (lung)	-0.30	0.20	-0.6-0.1	0.10
Primary Diagnosis (prostate)	0.20	0.30	-0.4-0.9	0.50
Alkaline phosphatase	-0.01	0.004	-0.02- -0.0001	0.05

Linear regression model to identify independent predictors

Linear regression analysis showed that the main diagnosis and alkaline phosphatase levels were significant independent predictors of serum calcium levels, with breast cancer patients being more likely to have lower levels of calcium levels and the higher the ALP levels, the lower the level of serum calcium(Table 6).

Gender analysis shows female predominance (55%) as compared to males (45%) (Figure 1).

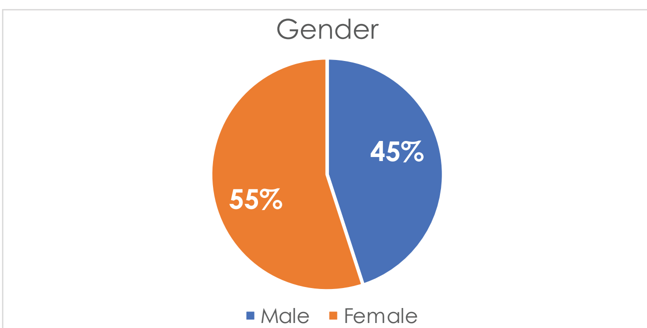

Figure 1: Gender Analysis of Patients (n=100)

DOI: https://doi.org/10.36283/ziun-pjmd 14-1/002

DISCUSSION

The study highlights multifaceted changes in serum calcium levels among metastatic bone cancer patients, reflecting significant calcium homeostasis imbalances. Both hypercalcemia and hypocalcemia were observed, consistent with previous studies. Up to 30% of patients with bone metastasis experience hypercalcemia, often linked to osteolytic activity in cancers. On the contrary, Rizzo et al. mentioned that hypocalcemia is very frequent in patients with disseminated osteoblastic lesions, such as prostate cancer[15]. Our findings showed that breast cancer patients had significantly lower serum calcium levels, with corrected calcium values markedly reduced compared to prostate cancer patients. This aligns with Darawshi et al. highlighting profound hypocalcemia in breast cancer due to increased osteoclastic activity linked to disease activity[15]. This highlights the need for careful monitoring of calcium levels in breast cancer patients, particularly as treatment changes can significantly impact metabolic dynamics.

The study found significantly higher ALP levels in blastic lesions compared to lytic lesions, reinforcing bone scans and greater metastatic involvement, emphasizing the need for clinical assessment of these biomarkers. Additionally corrected calcium levels decreased in early in metastatic states, aligning with Biodini et al.'s findings that increasing metastatic burden disrupts metabolic homeostasis[16]. By advancing cancer progression, patients may experience bone turnover and abnormality of calcium metabolism hence need the ability to adaptively manage these areas to proactively influence changes[17,18,19,20].

Linear regression analysis identified predictors of serum calcium levels, including primary diagnosis and ALP levels. A negative coefficient for breast cancer diagnosis and ALP suggests that breast cancer patients with higher ALP levels are more likely to have lower serum calcium, consisting with Generali et al.'s finding on bone metabolism changes in metastatic disease[21]. This highlights the importance of monitoring serum calcium and ALP in patients with metastatic bone cancer, particularly with the emergence of new therapies affecting bone remodeling.

This study has several limitations, including single-center data source, and a limited sample size that may not represent all cancer types or demographics. Key variables, such as renal function, dietary calcium intake, and medications, were not included but could impact calcium levels. Future studies should involve larger, multi-center cohorts and longitudinal designs to better validate results and understand serum calcium changes over time. Additionally, molecular insights into calcium dysregulation in cancer may lead to targeted therapies. Understanding patient profiles and treatment interactions with calcium metabolism is crucial for personalized management of calcium dysregulation in metastatic bone disease.

These findings highlight a gap in understanding calcium homeostasis in metastatic bone diseases. While hypercalcemia is well-studied, the clinical implications of hypocalcemia, particularly in prostate cancer, are less explored. These patients face the added challenge of low serum calcium levels and treatment-related bone complications[22,23,24,25]. The complexity of tumor biology and its interaction with the bone microenvironment requires incorporating bone health into treatment plans. Understanding the relationship between tumor biology, treatments, and metabolic effects, particularly calcium metabolism, is essential for developing personalized approaches and improving patient prognosis.

CONCLUSION

The study highlighted significant serum calcium dysregulation in metastatic bone cancers, with breast cancer patients exhibiting lower calcium levels due to osteoclastic activity. Elevated alkaline phosphatase levels in blastic lesions underscore its role as a marker of bone turnover. The progressive calcium decline from early to metastatic stage emphasizes the need for dynamic monitoring and tailored interventions. Further research on hypocalcemia is essential to enhance personalized management and improve patient outcomes.

LIST OF ABBREVIATIONS

ALP: Alkaline Phosphatase
PTH: Parathyroid Hormone
SD: Standard Deviation
WHO: World Health Organization

ACKNOWLEDGMENT

The authors acknowledge the institution for their immense support.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

The authors did not receive any funding.

ETHICAL APPROVAL

The ethical approval was obtained from ethical review board of the institution (No. IMC/ERB/2020-13).

AUTHOR CONTRIBUTION

MKM Conceptualization, data analysis, methodology, **SUM** Data analysis, methodology, editing the manuscript, **SD** Review of manuscript, data analysis, **AZ** Supervision, critical review, editing the manuscript, **MAM** Data collection, statistical analysis, **SAJ** manuscript writing, data interpretation, methodology.

REFERENCES

1. Arakil N, Akhund SA, Elaasser B, Mohammad KS. Intersecting Paths: Unraveling the Complex Journey of Cancer to Bone Metastasis. Biomedicines. 2024 May 13;12(5):1075. doi: 10.3390/biomedicines12051075..
2. Riquelme MA, Cardenas ER, Jiang JX. Osteocytes and Bone Metastasis. Front Endocrinol (Lausanne). 2020 Oct 14;11:567844. doi: 10.3389/fendo.2020.567844.
3. Elaasser B, Arakil N, Mohammad KS. Bridging the Gap in Understanding Bone Metastasis: A Multifaceted Perspective. Int J Mol Sci. 2024 Feb 29;25(5):2846. doi: 10.3390/ijms25052846.
4. Crooks M, Bendall S. Parathyroid hormone and vitamin D: from bench to bedside. Orthopaedics and Trauma. 2021 Oct 1;35(5):267-73.-doi.org/10.1016/j.mporth.2021.07.002.
5. Matikainen N, Pekkarinen T, Ryhänen EM, Schalin-Jäntti C. Physiology of Calcium Homeostasis: An Overview. Endocrinol Metab Clin North Am. 2021 Dec;50(4):575-590. doi: 10.1016/j.ecl.2021.07.005.
6. Yang Z, Yue Z, Ma X, Xu Z. Calcium Homeostasis: A Potential Vicious Cycle of Bone Metastasis in Breast Cancers. Front Oncol. 2020 Mar 10;10:293. doi: 10.3389/fonc.2020.00293.
7. Walker MD, Shane E. Hypercalcemia: A Review. JAMA. 2022 Oct 25;328(16):1624-1636. doi: 10.1001/-jama.2022.18331.
8. Nørregaard KS, Jürgensen HJ, Gårdsvoll H, Engelholm LH, Behrendt N, Søe K. Osteosarcoma and Metastasis Associated Bone Degradation-A Tale of Osteoclast and Malignant Cell Cooperativity. Int J Mol Sci. 2021 Jun 25;22(13):6865. doi: 10.3390/ijms22136865.
9. Darawshi S, Darawshi M, Naccache DD. Unusual hypocalcaemia in breast cancer relapse with multiple bone metastasis. Endocrinology, Diabetes & Metabolism Case Reports. 2022 Jan 1;2022(1). doi. 10.1530/EDM-20-0222.
10. Gonçalves JA, Costa T, Rema J, Pinto C, Magalhães M, Esperança A, Sousa L. Hypocalcemia in cancer patients: an exploratory study. Porto Biomedical Journal. 2019 Jul 1;4(4):e45. doi. 10.1097/j.pbj.0000000000000045.
11. Yanase Y, Bando H, Sato R, Matsuo T, Ueda A, Okazaki M, Hashimoto S, Iguchi-Manaka A, Hara H. Recurrent severe hypocalcemia following chemotherapy regimen changes in advanced breast cancer: two case reports. J Med Case Rep. 2024 Mar 25;18(1):150. doi: 10.1186/s13256-024-04478-3.
12. Zeng W, Swee DS. Severe and refractory hypocalcaemia secondary to osteoblastic bone metastases in bladder signet ring carcinoma: A case report and literature review. Medicine (Baltimore). 2022 Jul 1;101(26):e29731. doi: 10.1097/MD.0000000000029731.
13. Body JJ, Niepel D, Tonini G. Hypercalcaemia and hypocalcaemia: finding the balance. Support Care Cancer. 2017 May;25(5):1639-1649. doi: 10.1007/s00520-016-3543-1.
14. Baldessari C, Pipitone S, Molinaro E, Cerma K, Fanelli M, Nasso C, Oltrecolli M, Pirola M, D'Agostino E, Pugliese G, Cerri S, Vitale MG, Madeo B, Dominici M, Sabbatini R. Bone Metastases and Health in Prostate Cancer: From Pathophysiology to Clinical Implications. Cancers (Basel). 2023 Feb 28;15(5):1518. doi: 10.3390/cancers15051518.
15. Rizzo C, Vella S, Cachia MJ. Refractory hypocalcaemia complicating metastatic prostatic carcinoma. BMJ Case Rep. 2015 Jun 29;2015:bcr2015210003. doi: 10.1136/bcr-2015-210003.
16. Biondini M, Lehuédé C, Tabariès S, Annis MG, Pacis A, Ma EH, Tam C, Hsu BE, Audet-Delage Y, Abu-Thuraia A, Girondel C, Sabourin V, Totten SP, de Sá Tavares Russo M, Bridon G, Avizonis D, Guiot MC, St-Pierre J, Ursini-Siegel J, Jones R, Siegel PM. Metastatic breast cancer cells are metabolically reprogrammed to maintain redox homeostasis during metastasis. Redox Biol. 2024 Sep;75:103276. doi: 10.1016/j.redox.2024.103276.
17. Sturgeon KM, Mathis KM, Rogers CJ, Schmitz KH, Waning DL. Cancer- and Chemotherapy-Induced Musculoskeletal Degradation. JBMR Plus. 2019 Feb 25;3(3):e10187. doi: 10.1002/jbm4.10187.
18. Bartkiewicz P, Kunachowicz D, Filipski M, Stebel A, Ligoda J, Rembiałkowska N. Hypercalcemia in Cancer: Causes, Effects, and Treatment Strategies. Cells. 2024 Jun 18;13(12):1051. doi: 10.3390/-cells13121051.
19. Todenhöfer T, Stenzl A, Hofbauer LC, Rachner TD. Targeting bone metabolism in patients with advanced prostate cancer: current options and controversies. Int J Endocrinol. 2015;2015:838202. doi: 10.1155/2015/838202.
20. Jackmann N, Gustafsson J, Utriainen P, Magnusson P, Harila A, Atanasova D, Rinaldo C, Frisk P, Mäkitie O. Demographic and disease-related factors impact bone turnover and vitamin D in children with hemato-oncological diseases. JBMR Plus. 2024 Feb 24;8(4):ziae017. doi: 10.1093/jbmrpl/ziae017.
21. Generali D, Dovio A, Tampellini M, Tucci M, Tedoldi S, Torta M, Bonardi S, Allevi G, Aguggini S, Milani M, Harris AL, Bottini A, Dogliotti L, Angeli A, Berruti A. Changes of bone turnover markers and serum PTH after night or morning administration of zoledronic acid in breast cancer patients with bone metastases. Br J Cancer. 2008 Jun 3;98(11):1753-8. doi: 10.1038/sj.bjc.6604390.
22. Fekete Z, Ignat P, Jakab H, Todor N, László IP, Muntean AS, Curcean S, Nemeș A, Nuțu D, Kacsó G. Serum Calcium Level at Diagnosis Can Predict

Lethal Prostate Cancer Relapse. J Clin Med. 2024 Aug 16;13(16):4845. doi: 10.3390/jcm13164845.
23. Kc O, Dahal PH, Koirala M, Kothagundla CS, Al Zaghal E, Fahed R. A Case of Recurrent Severe Hypocalcemia with Prolonged Hospitalization and Readmissions After Single Dose of Denosumab in Metastatic Prostate Cancer Patient. J Community Hosp Intern Med Perspect. 2022 Apr 12;12(2):60-64. doi: 10.55729/2000-9666.1043.
24. Gouli S, Wang J, Patel A, Allerton J. Hypocalcemia in a Patient With Metastatic Prostate Cancer From Denosumab Treatment. Cureus. 2021 Aug 10;13(8):e17046. doi: 10.7759/cureus.17046.
25. Ardura JA, Álvarez-Carrión L, Gutiérrez-Rojas I, Alonso V. Role of Calcium Signaling in Prostate Cancer Progression: Effects on Cancer Hallmarks and Bone Metastatic Mechanisms. Cancers (Basel). 2020 Apr 25;12(5):1071. doi: 10.3390/cancers12051071.