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Frequency of Hypocalcaemia in Cancer Patients Receiving Zoledronic Acid for Bone Metastasis

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ABSTRACT

Background: The use of zoledronic acid for bone metastases in cancer patients is frequently accompanied by hypocalcemia, potentially compromising outcomes and quality of life. Despite its clinical significance, there is limited comprehensive data on the incidence and associated risk factors in this population. **Objectives:** To determine the frequency of hypocalcemia in cancer patients receiving zoledronic acid therapy for bone metastases and to assess its association with demographic and clinical variables. **Study Settings:** The research was undertaken at Shaukat Khanum Memorial Cancer Hospital & Research Center in Lahore, specifically in the Department of Medicine. **Duration of Study:** July 2024 to December 2024. **Data Collection:** A prospective observational cross-sectional study included 180 cancer patients aged 18–60 years with bone metastases receiving zoledronic acid therapy for at least three months. Corrected serum calcium levels were measured to define hypocalcemia (<8.5 mg/dl). Data were stratified by age, gender, BMI, and cancer type, and analyzed using SPSS version 21. **Results:** The prevalence of hypocalcemia was 6.7%. Hypocalcemia rates were comparable across age groups (6.6% in 18–50 years vs. 7.0% in >50 years; p = 0.926), genders (4.3% in males vs. 9.1% in females; p = 0.202), BMI categories (7.0% in BMI 18–25 vs. 6.4% in BMI >25; p = 0.873), and cancer types (breast cancer: 5.7%; lung cancer: 6.7%; prostate cancer: 6.4%; renal cell carcinoma: 9.1%; p = 0.936). **Conclusion:** Hypocalcemia is a rare but significant complication of zoledronic acid therapy. Routine calcium monitoring is essential for early detection and management. Future research should identify risk factors and improve supplementation.

INTRODUCTION

Advanced cancer often leads to a reduction in strength of bone because of osteoporosis, metastasis, or bone loss due to treatment, which can result in critical skeletal complications.[1-4] A notable decline in life quality accompanies these changes, as patients face an increased risk of fractures, excruciating pain in bone, hypercalcemia of malignancy, and compression of spinal cord. Advanced bone metastases often signal deteriorating health and reduced survival rates.[5] The occurrence of skeletal-related events often signals a decline in quality of life. Fractures, limit mobility, may cause pain, and impair function. In patients with bone metastases, these events are closely linked to a heightened risk of mortality and poor outcomes.[5] Zoledronic acid remains the cornerstone of metastatic bone disease treatment, firmly established as the gold standard.[6]

The treatment's main objectives include preventing skeletal-related events, managing osteoporotic issues, and alleviating bone pain. Among bisphosphonates, zoledronic acid is uniquely effective in reducing skeletal-related events in bone metastases from advanced renal cell carcinoma and prostate cancer. Zoledronic acid serves dual purposes in prostate cancer, preventing bone loss in patients with locally advanced disease on androgen deprivation therapy and minimizing skeletal-related events in men with hormone-sensitive or hormone-refractory metastatic disease.[7] Zoledronic acid is both safe and well-tolerated, demonstrating effectiveness in significantly lowering the incidence, delaying the onset, and reducing the risk of skeletal-related events. It is the only bisphosphonate approved for addressing skeletal complications in patients with bone metastases across all solid tumors.[8]

Zoledronic acid therapy is associated with frequent adverse events, including back pain (12%), fatigue (14%), nausea (14%), and arthralgia (20%), affecting more than 10% of patients.[9] Less common effects, such as asthenia, fever, vertigo, and renal tubular necrosis, have also been reported. Patients up to 20 percent experience flu-like symptoms—fever, myalgia, and fatigue—typically following the first dose. Hypocalcemia, a significant concern, has been highlighted in several case reports and observational studies.

Nasser et al[10] reported a 6.1% hypocalcemia in cases received treatment with zoledronic acid for bone metastases. This study is driven by the lack of comprehensive literature on the incidence of hypocalcemia in cancer patients undergoing treatment with zoledronic acid for bone metastases. The findings will help quantify the burden of hypocalcemia, guiding future research on risk factors, early diagnosis, and effective management strategies in metastatic disease.

METHODOLOGY

The study, designed as a six-month prospective observational cross-sectional investigation, was conducted in the Shaukat Khanum Memorial Cancer Hospital & Research Center in Lahore. Following synopsis approval, a sample size of 180 patients was calculated based on a reported 6.1% prevalence of hypocalcemia, using a 95% confidence interval and a 3.5% margin of error. Participants were recruited through non-probability consecutive sampling.

This study targeted patients aged 18 to 60 years with cancer and bone metastases, all of whom had been receiving zoledronic acid therapy for a minimum of three months. Patients with chronic kidney disease (CKD) (serum creatinine more than 1.3 mg/dl) or a BMI above 35 were excluded. A total of 180 participants met the inclusion criteria after screening. Venous blood samples were obtained from patients during outpatient and emergency department visits or hospital stays to measure corrected serum calcium levels. Hypocalcemia was classified as corrected serum calcium below 8.5 mg/dl. Data were recorded on a structured pro forma and computed through SPSS. Frequencies and percentages were calculated for categorical variables such as gender and hypocalcemia, while mean and standard deviation were used for continuous variables like age. Stratification was performed based on cancer type, zoledronic acid therapy duration, age, gender, and BMI, and chi-square tests were applied to evaluate statistical significance, with a p-value < 0.05 considered significant.

RESULTS

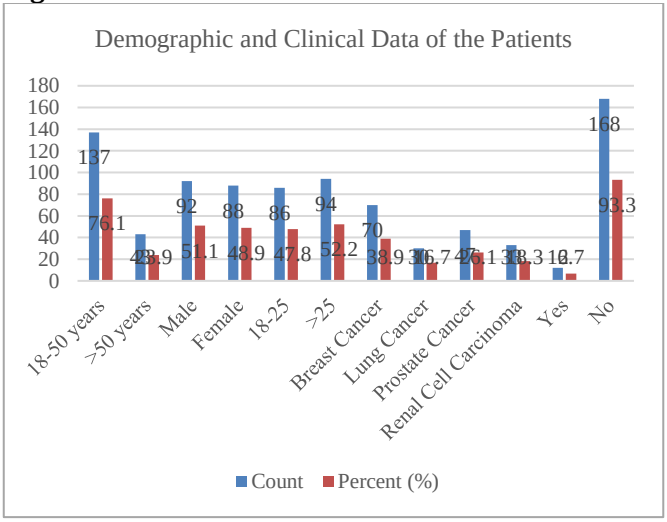
In this study (76.1%) cases had the age range 18-50 years, whereas >50 years old cases were 23.9%. Gender distribution showed a slightly lower proportion of females (48.9%) compared to (51.1%) male cases. Regarding body mass index (BMI), 47.8% of patients had a BMI in the normal range (18–25), while 52.2% were classified as overweight or obese (BMI >25). The types of cancer observed included breast cancer (38.9%), lung cancer (16.7%), prostate cancer (26.1%), and renal cell carcinoma (18.3%). Hypocalcemia, a clinical condition being studied, was found in only 6.7% of the patients, whereas 93.3% did not experience this condition.

Table 1

Demographic and Clinical Data of the Patients (n=180)

Variable	Group	Count	Percent (%)
Age	18-50 years	137	76.1
	>50 years	43	23.9
Gender	Male	92	51.1
	Female	88	48.9
BMI	18-25	86	47.8
	>25	94	52.2
Type of Cancer	Breast Cancer	70	38.9
	Lung Cancer	30	16.7
	Prostate Cancer	47	26.1
	Renal Cell Carcinoma	33	18.3
Hypocalcaemia	Yes	12	6.7
	No	168	93.3

Figure 1



This table evaluates the frequency of hypocalcemia among cancer patients receiving zoledronic acid for bone metastases, stratified by different demographic and clinical variables.Among patients aged 18–50 years, 6.6% developed hypocalcemia, compared to 7.0% in those older than 50 years. The difference was not statistically significant (p = 0.926). Hypocalcemia occurred in 4.3% of male patients and 9.1% of female patients, but the difference did not reach statistical significance (p = 0.202). Patients with a BMI between 18 and 25 had a hypocalcemia prevalence of 7.0%, while those with a BMI >25 had a slightly lower prevalence of

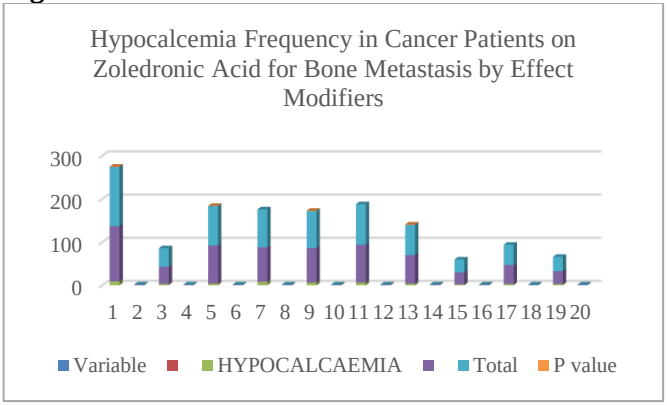
6.4%. (p=0.873). Among the different cancer types, the prevalence of hypocalcemia was 5.7% in breast cancer, 6.7% in lung cancer, 6.4% in prostate cancer, and 9.1% in renal cell carcinoma. Again, no significant differences were observed across the cancer types (p = 0.936). Overall, hypocalcemia was infrequent and showed no significant variation across the studied effect modifiers, suggesting a consistent pattern in its occurrence irrespective of age, gender, BMI, or cancer type.

Table 2

Frequency of Hypocalcaemia in Cancer Patients Receiving Zoledronic Acid for Bone Metastasis According to Various Effect Modifiers

Variable		Hypocalcaemia		Total	P value
Age(years)	18-50	9 6.6%	128 93.4%	137 100.0%	0.926
	>50	3 7.0%	40 93.0%	43 100.0%	
Gender	Male	4 4.3%	88 95.7%	92 100.0%	0.202
	Female	8 9.1%	80 90.9%	88 100.0%	
BMI	18-25	6 7.0%	80 93.0%	86 100.0%	0.873
	>25	6 6.4%	88 93.6%	94 100.0%	
Type of Breast Cancer	Breast Cancer	4 5.7%	66 94.3%	70 100.0%	0.936
	Lung Cancer	2 6.7%	28 93.3%	30 100.0%	
	Prostate Cancer	3 6.4%	44 93.6%	47 100.0%	
	Renal Cell Carcinoma	3 9.1%	30 90.9%	33 100.0%	

Figure 2



DISCUSSION

The findings of our study contribute to the understanding of hypocalcemia as a significant complication in cancer patients receiving zoledronic acid for bone metastases. Integrating insights from recent literature, we explore the incidence, risk factors, and clinical implications of hypocalcemia, providing a comprehensive context for its management.

Our study observed a prevalence of hypocalcemia of 6.7%, consistent with findings from other studies. Paul. S et al.[11] reported a higher prevalence (25%) among patients treated with bone-modifying agents (BMAs), with 8.8% experiencing severe hypocalcemia (grade ≥3). Similarly, Chennuru et al[12] identified hypocalcemia in 35% of patients treated with zoledronic acid, suggesting a wide variation based on study design and patient populations. Al Elq AH[13] emphasized that asymptomatic hypocalcemia, while less common, can become symptomatic in the presence of predisposing factors such as vitamin D deficiency. These findings reinforce the need for vigilant monitoring of calcium levels in patients undergoing treatment with BMAs.

Our results showed no statistically significant differences in hypocalcemia prevalence across demographic and clinical subgroups, including age, gender, BMI, and cancer type. However, other studies highlight specific risk factors. Paul S. et al[9] and Jean-Jacques Body et al[14] identified vitamin D deficiency, hematologic malignancies, reduced creatinine clearance, and higher baseline bone turnover markers as significant predictors of hypocalcemia. Al-Elq-AH[13] and Body[11] also emphasized the critical role of vitamin D in preventing hypocalcemia, particularly in populations with widespread deficiency.

Chennuru et al[12] reported that hypomagnesemia, renal impairment, and prolonged zoledronic acid elimination half-life may exacerbate hypocalcemia. Similarly, Jean-Jacques Body[14] found that denosumab, another potent antiresorptive agent, has a higher incidence of hypocalcemia compared to zoledronic acid (12.4% vs. 5.3%), likely due to its greater antiresorptive effect. This highlights the need for caution when selecting bone-targeted therapies, particularly in patients with multiple bone metastases or pre-existing risk factors.

The clinical implications of hypocalcemia are substantial, as it may exacerbate skeletal-related events and negatively impact patient quality of life. Body et al[14] and Al Elq AH[13] emphasized the importance of correcting serum calcium and vitamin D levels before initiating treatment with BMAs. In our study, routine monitoring of calcium levels was conducted, but vitamin D levels were not assessed, representing a limitation.

The studies by Fei Ma[15] and Body further underscore the broader context of bone health management in cancer patients. Beyond the prevention of skeletal complications, effective management strategies should address adverse drug reactions such as hypocalcemia to improve patient outcomes.

Future research should aim to identify additional risk factors for hypocalcemia, including genetic predispositions and other biochemical markers. Multi-center studies with larger sample sizes and diverse populations could provide more generalizable insights. Moreover, investigating strategies to optimize vitamin D and calcium supplementation protocols could further reduce hypocalcemia incidence.

CONCLUSION

Hypocalcemia remains a manageable but clinically significant complication of zoledronic acid therapy. By integrating findings from this and previous studies, clinicians can better identify at-risk patients and implement preventive measures to enhance treatment outcomes and patient quality of life.

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