Hypocalcemia in Patients With Osteoporosis and Normal Renal Function, Treated With Denosumab, a Retrospective Analysis

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ABSTRACT

OBJECTIVE: The reported hypocalcemia in postmenopausal women with osteoporosis who received Denosumab was low (0.05%-1.7% to 7.4%). The major prediction factors were vitamin D and calcium levels and renal function. The objective is to evaluate the incidence of hypocalcemia in patients with osteoporosis, normal renal function, and vitamin D who received Denosumab.

METHOD: A retrospective analysis was conducted using the medical records (2022-2023). We looked for hypocalcemia (albumin-adjusted calcium lower than 2.2 mmol/L).

RESULTS: Two hundred one postmenopausal women diagnosed with osteoporosis and received denosumab treatment were included. All patients received vitamin D3 capsules and calcium supplementation. The mean age of the patient was 75.7 ± 7.0 years (56-91 years). Hypocalcemia was observed in 46 (23%) patients following a subcutaneous dose of Denosumab 60 mg. Median calcium was 2.25 mmol/L (minimum: 0.890 mmol/L, maximum: 2.6 mmol/L). Fourteen (30.4%) patients had severe hypocalcemia (<1.8 mmol/L) and required parenteral correction. A comparison between hypocalcemia and patients with normal calcium indicated that the significant predictor of hypocalcemia was pretreatment parathyroid hormone levels (9.9 ± 11.8vs 7.6 ± 2.56 pmol/L, respectively; $P < .005$). The prognostic role of parathyroid hormone for the denosumab-associated hypocalcemia was assessed using ROC curve analysis. For the cut-off value of Parathyroid hormone = 6.8 pmol/L, giving serum parathyroid measurement an AUC of 0.668 (0.599-0.737) - $P = .0007$; sensitivity 85%; specificity 52%.

CONCLUSION: Hypocalcemia induced by the denosumab treatment is more prevalent than previously shown in patients with osteoporosis receiving adequate calcium and vitamin D supplements. An elevated parathyroid hormone predicts hypocalcemia related to denosumab therapy in patients with normal calcium and vitamin D levels.

KEYWORDS: Denosumab, osteoporosis, hypocalcemia, hypophosphatemia, postmenopausal

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Introduction

Denosumab is a human monoclonal antibody to the kappa-B nuclear ligand activating receptor (RANKL), a tumor necrosis factor (TNF) receptor superfamily member. It is essential for the differentiation of monocytes into osteoclasts. It decreases bone resorption, reduces fracture risk, inhibits osteoclast formation, and increases bone mineral density (BMD).[1] Denosumab improves the density in women with low BMD and reduces fracture risk.[2]

Preexisting hypocalcemia is a relative contraindication for denosumab therapy unless corrected. All women undergoing denosumab therapy should receive daily vitamin D (400-800 international units) and calcium (1000-1200 mg).[3] Thus, hypocalcemia is not a common problem in patients with normal renal function adequately treated with calcium and vitamin D. A small proportion of postmenopausal women in denosumab trials had a decrease in their serum calcium level to <2.1 mmol/L; 1.7%versus 0.4% in the placebo group.[3]

However, patients with chronic kidney disease or hypoparathyroidism predispose them to symptomatic hypocalcemia (albumin-adjusted calcium level of less than 2.0 mmol/L) and require treatment.[4] The rate of symptomatic hypocalcemia was higher in 10% and 29% of patients with reduced renal function, and creatinine clearance was 50 to 80 and <30 mL/min, respectively.[4] Hypocalcemia also occurred in 29% of patients on hemodialysis.[4] The lowest point in serum calcium occurs approximately 10 days after denosumab injection. In the present study, we included premenopausal patients without normal

renal function. The major prediction factors for hypocalcemia in denosumab-treated patients were vitamin D and calcium levels and renal function prior to administration. Therefore, we aim to assess the incidence of hypocalcemia in patients with osteoporosis treated with Denosumab, with normal renal function, vitamin D, and calcium.

Materials and Methods

A retrospective, observational, single-center study was conducted in Ahmadi general hospital, Kuwait, from first January 2022 till January 2023. The ethics committee of Ahmadi Hospital approved the study and there is no ethical issue. Being a retrospective analysis with data collection from medical records, the Ahmadi ethics committee waived the need for written informed consent. The data sheet information from the electronic medical records included age, weight, height, body mass index, previous medical history of fracture, smoking, drug use, steroid therapy, and other associated diseases, such as autoimmune arthritis, hypertension, ischemic heart disease, and diabetes mellitus. In addition, as part of follow-up, the serum levels of albumin, calcium, phosphorus, alkaline phosphatase, parathyroid hormone, and eGFR at baseline and 1 to 2 weeks were documented 1 month and 3 months after treatment.

The inclusion criteria were patients with osteoporosis and older than 55 years of age who had received a subcutaneous dose of Denosumab 60 mg (Prolia; Amgen company, USA) and daily supplementation of vitamin D. To avoid hypocalcemia, Vitamin D3 (cholecalciferol) capsule and calcium supplementation was given to all patients with denosumab therapy (3). Patient should have normal renal function (defined as normal estimated Glomerular filtration rate (eGFR $\geq$ 90 mL/min/1.73 m^2) and creatinine, or mild abnormal (eGFR 60-89 mL/min/1.73 m^2) or mild to moderately abnormal kidney disease (45-59 mL/min/1.73 m^2).[5] Blood sampling was taken at baseline, 1-2 weeks, and 4 weeks after denosumab administration was essential for inclusion.

Exclusion criteria were if patients,

1. had adjusted abnormal baseline serum calcium concentrations. The normal range in our laboratory is (2.2-2.6 mmol/L);
2. Moderately severe (30-44 mL/min/1.73 m^2) or severe chronic kidney diseases (15-29 mL/min/1.73 m^2). Chronic kidney disease is defined as decreased kidney function for 3 or more months, irrespective of cause. (eGFR $<$44 mL/min/1.73 m^2) or on hemodialysis[5]; primary hyperparathyroidism; active malignant tumors; invasive dental procedures
3. Received therapy that could affect serum calcium concentration (Cinacalcet, Foscarnet, Chemotherapy such as cisplatin and Combination therapy with fluorouracil and leucovorin).
4. with a fresh fracture or underwent orthopedic surgery within a month before denosumab administration.

Hypocalcemia was an adjusted serum calcium concentration to an albumin level of less than 2.2 mmol/L. The formula used in corrected calcium concentration was corrected Ca = [0.02 $\times$ (normal albumin − patient's albumin)] + serum Ca level. Only the drop in serum calcium level after the first dose was used to diagnose hypocalcemia in patients who received Denosumab more than once within the study period. The eGFR level was calculated for all patients, and normal eGFR was included. The primary endpoint was to determine the change in serum calcium concentration over time following the initial denosumab injection.

Of the initial retrospective study, 220 patients were included in the current study.

Data collection

Statistics analysis. The statistical analyses were performed using Statistical Package for the Social Sciences version 19.0 (SPSS Inc). Continuous variables are shown as mean and standard deviation or median and range. Categorical variables are presented as numbers and percentages. *T*-tests were used to compare continuous variables, and chi-square or Fisher's exact tests were used to compare categorical variables between study groups. A 2-sided *P*-value of less than .05 was considered significant. Receiver operating characteristic (ROC) curves were determined, charting sensitivity to 1–specificity to measure predictive performance for parathyroid hormone and calcium level after denosumab therapy in the study group. The closer the area under the curve (AUC) to 1, the better the predictive performance. Optimum cut-off values, specificity, sensitivity, and positive and negative predictive values were obtained for total serum parathyroid level.

Results

Two hundred twenty patients with osteoporosis received denosumab treatment plus prophylactic vitamin D3 (cholecalciferol) at baseline (Figure 1). The mean patient age was 75.7 $\pm$ 8.0 years (56-91 years). There were 201 women (91%) included in the study. Patient characteristics are summarized in (Table 1). Of these, 45 patients (20%) had a history of neck femur or vertebral fracture—total knee replacement (10 patients, 4%). In addition, patients had disorders such as autoimmune arthritis (12 patients, 5%), DM (39 patients, 19%), hypertension (77 patients, 38%), liver cirrhosis (6 patients, 2%), and hypothyroidism (36 patients, 16%). In addition, there were 23 patients (11%) had managed osteoporosis, including bisphosphonate (13 patients, 7%), a selective estrogen receptor modulator (4 patients, 2%), or teriparatide (6 patients, 2.4%).

Baseline serum alkaline phosphatase, albumin, and calcium levels were normal. The PTH value was elevated in 114 (57%) patients, significantly elevated in the group that developed hypocalcemia (9.9vs 7.6, *P*: .005). Phosphate was reportedly severely low in 8 cases (4%), requiring parenteral correction and normal calcium levels.

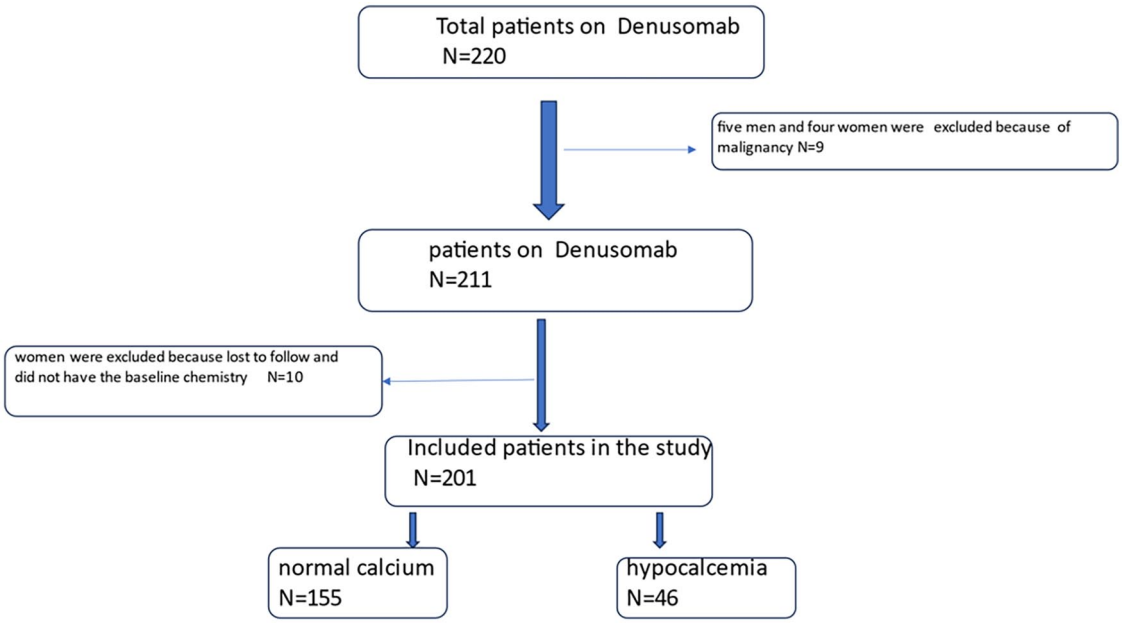

Figure 1. Showing flow-chart.

Table 1. The characteristics and distribution of lab results of patients with and without denosumab-induced hypocalcemia.

	NORMAL CALCIUM (N 155)	HYPOCALCEMIA N 46	*P* VALUE
Age	60.7 ± 7.9	55.8 ± 8.1	.968
DM (%)	30 (19)	9 (19)	
Hypertension (%)	57 (36)	20 (43)	
Ischemic heart disease (%)	44 (28)	14 (30)	
T score			
Lumbar spine	2.82 ± 0.70	2.84 ± 0.69	
Total hip –	1.89 ± 0.81	1.91 ± 0.81	
Femoral neck –	2.15 ± 0.72	2.17 ± 0.71	
Bisphosphonate, n (%)	12 (19.0)	2 (9.1)	.278
Calcium (mmol/L)	2.37 ± 0.277)	1.8 ± 0.349	.001
Albumin (g/L)	35	35	
Alkaline phosphatase (U/L)	288.3 ± 110.6	278.4 ± 102.1	.702
PTH (pmol/L)	7.6 ± 2.56	9.9 ± 11.8	.005
eGFR (mL/min/1.73 m^2)	71.4 ± 15.4	67.6 ± 18.0	.389
Vitamin D (ng/mL)	60.9 ± 11.6	59.4 ± 11.8	.7
Phosphate (mmol/L)	1.3 ± 0.2	1.2 ± 0.34	.2
Day on which blood sample was drawn after administration of denosumab (median day [IQR])			
1-2 wk	7.0 (7.0-7.0)	7.0 (7.0-7.0)	.737
1 mo	28.0 (29.0-28.0)	28.0 (27.0-31.0)	.084

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; Plus–minus values are means ± SD.

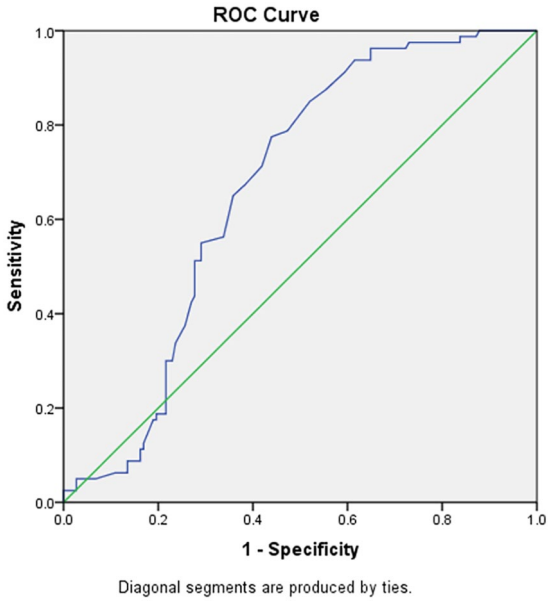

Figure 2. ROC curve for parathyroid hormone.

Normal or mild renal dysfunction (eGFR: >60 mL/min/1.73 m^2) was noticed in 150 patients (75%), whereas 51 patients (25%) had mild to moderate kidney dysfunction (45-59 mL/min/1.73 m^2).

None of the patients had hypocalcemia at baseline, but 46 (23%) reported hypocalcemia following a subcutaneous injection of Denosumab 60 mg with a median calcium level of 2.25 (minimum: 0.890, maximum: 2.6).

Thirty-two (69.5%) of the patients with mild hypocalcemia (⩾1.8 mmol/L), and 14 (30.4%) were severe and required parenteral therapy (<1.8 mmol/l). Mild Hypocalcemia was corrected with oral calcium supplementations (1000-3000 mg/daily). All hypocalcemia patients had elevated PTH. Receiver operating characteristic (ROC) curves were plotted to assess the value of parathyroid (Figure 2) as a predictive marker for hypocalcemia. A cut-off point of (6.8 pmol/L) was determined by using the ROC method, giving serum parathyroid measurement an AUC of 0.668 (0.599-0.737) - P= .0007; sensitivity 85%; specificity 52%; positive likelihood ratio 4 and a negative likelihood ratio of 0.46.

Discussion

Hypocalcemia related to denosumab therapy has been reported in several studies on different diseases. The incidence of hypocalcemia induced by denosumab was 14% (95% CI 9.1-20.7) within 6 months of treatment, although they were on appropriate calcium/cholecalciferol therapy.[6] Stages 4 and 5 CKD and male sex were associated with subsequent hypocalcemia.[6] In the FREEDOM trial, hypocalcemia was defined as an albumin-adjusted calcium level of less than 8.0 mg per deciliter (2.0 mmol/L) in fasting specimens drawn just before injection of the study drug.[2] There was no reported hypocalcemia in the denosumab arm compared to the placebo group 0.1% (3 cases). In AMG 162 Bone Loss Study Group, the mean albumin-adjusted serum calcium levels in denosumab-treated subjects demonstrated early but small decreases from baseline compared to the placebo and alendronate groups.[7] Six subjects receiving denosumab (1.9%) had albumin-adjusted serum calcium levels that fell below the reference range. The lowest recorded value (1.95 mmol/L) occurred at 2 months in a subject who received 14 mg of denosumab every 6 months.[7] Other studies did show no notable changes in mean albumin-adjusted serum calcium concentration, and no trends in serum chemistry or hematology parameters were noted during the off-treatment phase.[8] All the above studies were not protocolized calcium monitoring after administration of denosumab.

The incidence of hypocalcemia was higher in the present study, which may be related protocolized checking calcium level after therapy and to low parathyroid hormone levels. A previous retrospective study was conducted based on medical records (2010-2018), and denosumab-induced hypocalcemia developed during treatment in 7.4% of patients (1% less than 8 mg/dL). The pretreatment levels of serum creatinine and calcium were the strongest predictors of hypocalcemia. The hypocalcemia events increased in strong correlation with a decrease in eGFR.[9]

In a prospective study of 288 women and 44 men with osteoporosis aged ⩾60 years, the incidence of hypophosphatemia and calcium was not reported to be well maintained in 1 year,[10] which was in keeping with other results.[11] However, in another prospective study, hypophosphatemia was observed in 7 patients among 31 women with osteoporosis.[12] Our study showed 8 cases, and 3 of them required parenteral correction.

Inhibition of osteoclastic bone resorption is the underlying mechanism for developing denosumab-induced hypocalcemia, leading to hypocalcemia by decreasing calcium mobilization from the bone into the bloodstream.[2] In the state of vitamin D deficiency, there will be a large population of osteoblasts, leading to excess calcium shifting into bone.[13] Hypocalcemia is associated with a compensatory PTH elevation. Impairment of the secretion in PTH or resistance to PTH action at the level of bone and kidney in patients with CKD may lead to hypocalcemia.[14]

In the current study Although giving serum parathyroid measurement an AUC of 0.668, means inadequate discrimination, it is of good sensitivity 85% but poor of poor specificity 52%. The parathyroid hormone (PTH) levels had been measured frequently in the absence of hypercalcemia in patients undergoing an evaluation for low bone density, vitamin D deficiency, or other conditions. An international panel of experts recognized this phenotype of primary hyperparathyroidism HPT in which PTH levels are consistently elevated, but serum total and ionized calcium levels are normal.[15] The secondary causes for hyperparathyroidism should be excluded, for example, chronic kidney disease, decreased calcium intake, malabsorption, vitamin D deficiency, bariatric surgery, renal calcium loss, and certain medications (loop diuretics, bisphosphonates & Denosumab).[16] Normal serum calcium with elevated parathyroid hormone (PTH) is normocalcemic hyperparathyroidism (HPT). Autonomous secretion of PTH from the

parathyroids can lead to normocalcemic primary hyperparathyroidism (PHP). In normocalcemic secondary hyperparathyroidism (HPT), PTH secretion increases as a reflex to a low calcium stimulus.[15,16]

The evaluation of patients who may receive Denosumab is the same as recommended for all patients with osteoporosis, for example, complete blood count, complete chemistry profile (including alkaline phosphatase), calcium, phosphorus, and 25-hydroxyvitamin D.[17] Physicians tend not to check the parathyroid hormone levels in patients with normal serum calcium levels. Therefore, correcting hypocalcemia and hypovitaminosis D before starting denosumab therapy is essential. In addition, all patients should be supplemented with vitamin D and calcium while on denosumab therapy.[18] Recently, osteoporosis and metabolic bone disease clinics have been proactively evaluating potential bony defects in patients at risk of high bone resorption from metastatic bone disease or secondary hyperparathyroidism, and normocalcemic hyperparathyroidism conditions have been detected.[18,19]

The limitation of our study is the small number of selected patients, as we selected only a specific population of osteoporotic patients with normal or borderline renal function. In addition, only the lowest value of calcium measurement was obtained in each predefined period; therefore, we could not assess the course of hypocalcemia through a certain period.

In conclusion, denosumab-induced hypocalcemia is more prevalent than previously shown in patients with osteoporosis with adequate calcium supplementation, normal renal function, and vitamin D therapy. In addition, hyperparathyroidism may be a predictive factor in patients with normal calcium and vitamin D levels.

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Authors' Contributions

Z B wrote the article, and A H collected the data; OM, MJ, MZ, and AF shared in the discussion and revision of the manuscript. ZB performed the statistical analyses.All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Ethical Approval

No ethical approval was required as this study did not involve human participants or laboratory animals.

There is no ethical issue.

Consent for Publication

Patients and the public were not involved in this research's design, conduct, reporting, or dissemination plans. Therefore, patient consent for publication was not required.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon request.

Disclosure

The research was performed as part of the employment of the authors in the Kuwait Oil Company.

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