Int. J. Pharm. Investigation, 2023; 13(4):789-792.
https://www.jpionline.org

Original Article

Denosumab-induced Hypocalcemia in Patients with Osteoporosis and Normal Renal Function

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ABSTRACT

Introduction: The reported hypocalcemia was low in denosumab-treated postmenopausal women with osteoporosis (0.05–1.7% to 7.4%). The major prediction factors were Vitamin D and calcium levels and renal function. **Aim:** To assess the rate of hypocalcemia in patients with osteoporosis treated with denosumab, with normal renal function and Vitamin D. **Materials and Methods:** A retrospective analysis was conducted using the medical records (2021–2022). We looked for hypocalcemia (albumin-adjusted calcium lower than 2.1 mmol/L). **Results:** We included 201 women with postmenopausal osteoporosis who received denosumab treatment plus prophylactic Vitamin D_3 capsules. The mean age of the patient population was 75.7 ± 7.0 years (56–91 years). Hypocalcemia was observed in 46 (23%) patients following a single 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 cases (< 1.8 mmol/L) and required parenteral correction. A comparison between hypocalcemia and patients with normal calcium indicated that the strongest predictors of hypocalcemia were pretreatment parathyroid hormone levels (9.9 ± 0.5 vs. 7.6 ± 0.5 pg/L, respectively; $p<0.005$). Eight patients (3.3%) developed hypophosphatemia. The baseline serum albumin, calcium, and alkaline phosphatase levels were normal. **Conclusion:** The denosumab-associated hypocalcemia is more prevalent than previously shown in patients with osteoporosis receiving adequate calcium and Vitamin D supplementation. An elevated parathyroid hormone is an important predicting factor in patients with normal calcium and Vitamin D levels.

Keywords: Denosumab, Osteoporosis, Hypocalcemia.

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Received: 10-03-2023;
Revised: 28-04-2023;
Accepted: 26-05-2023.

INTRODUCTION

The human monoclonal antibody, denosumab, to Receptor Activator of Nuclear Factor-κB Ligand (RANKL), a member of the Tumor Necrosis Factor (TNF) receptor superfamily, is essential for osteoclastogenesis. It reduces fracture risk, inhibits osteoclast formation, decreases bone resorption, and increases Bone Mineral Density (BMD).[1]

In postmenopausal women with low BMD, denosumab improves Bone Mineral Density (BMD) and reduces fracture risk.[2]

Preexisting hypocalcemia is a relative contraindication for denosumab therapy unless corrected. All women undergoing denosumab therapy should be supplemented with daily calcium (1000 mg) and Vitamin D (400 to 800 international units). Thus, hypocalcemia is typically not a concern in patients with normal renal function adequately supplemented with calcium and Vitamin D. A small proportion of postmenopausal women in denosumab trials had a decrease in their serum calcium level to <8.5 mg/dL (2.1 mmol/L; 1.7 versus 0.4% in the placebo group).[3]

However, patients with conditions predisposing them to hypocalcemia, such as chronic kidney disease or hypoparathyroidism, usually have symptomatic hypocalcemia and require treatment.[4] The rate of symptomatic hypocalcemia was higher in 10% and 29% of subjects when creatinine clearance was 50–80 and <30 mL/min, respectively.[4] Hypocalcemia also occurred in 29% of patients on hemodialysis.[4] The nadir in serum calcium occurs approximately ten days after denosumab administration. In the present study, we included premenopausal patients without normal renal function. The major prediction

DOI: 10.5530/ijpi.13.4.098

factors for hypocalcemia in denosumab-treated patients were Vitamin D and calcium levels and renal function prior to administration. We aim to assess the rate of hypocalcemia in patients with osteoporosis treated with denosumab, with normal renal function, calcium and Vitamin D.

MATERIALS AND METHODS

Hypocalcemia was an adjusted serum calcium concentration to an albumin level of less than 2.2 mmol/L. For example, if the serum albumin level was 40 gm/L, the corrected calcium level was calculated according to the following equation: corrected serum calcium=serum calcium (mmol/L)-serum albumin (g/L) + 4.0. Only the drop in serum calcium level after the first administration was used to determine hypocalcemia in patients given denosumab several times 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.

The inclusion criteria were patients with osteoporosis and 55 years of age who had received a subcutaneous dose of denosumab 60 mg (Prolia; Amgen company, USA) and daily supplementation of Vitamin D. In our institution; we use a Vitamin D_3 (cholecalciferol) capsule as a prophylactic drug for denosumab to avoid hypocalcemia. A routine blood sampling at baseline, 1–2 weeks, and one month after denosumab administration was essential for inclusion.

Exclusion criteria were if patients;

1. Had adjusted abnormal baseline serum calcium concentrations. The normal range observed in our laboratory (2.2–2.6 mmol/L);

2. Had severe CKD (eGFR, 30 mL/min) or on hemodialysis; primary hyperparathyroidism; active malignant tumors; invasive dental procedures;

3. Received calcitonin replacement therapy or other medications that could affect serum calcium concentration;

4. With a fresh fracture or underwent orthopedic surgery within a month before denosumab administration;

5. Had surgery during the first course of denosumab.

Of the initial retrospective study, 220 patients were eligible for the current study. The study was conducted with the approval of the ethics committee of Ahmadi Hospital. The ethics committee waived the need for written informed consent because this is a retrospective study with data collection and analysis from medical records.

Data collection

The data were collected from the Ahmadi Hospital Electronic Medical Record (EMR) system. The data sheet information obtained from the EMR included age, weight, height, Body Mass Index (BMI), previous fracture history, special habits such as smoking history, drug use, glucocorticoid use, other associated diseases, such as rheumatoid arthritis, hypertension, ischemic heart disease, and diabetes mellitus, and prior treatment for osteoporosis. In addition, as part of follow-up, the serum levels of albumin, calcium, phosphorus, alkaline phosphatase, parathyroid hormone, and eGFR at baseline and 1–2 weeks were documented one month and three months after treatment.

Statistical analysis

The statistical analyses were performed using SPSS 19. Continuous variables are shown as either 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 two-sided *p*-value of less than 0.05 was considered significant.

RESULTS

Two hundred twenty patients with osteoporosis received denosumab treatment plus prophylactic Vitamin D_3 (cholecalciferol) at baseline. The mean patient age was 75.7 ± 8.0 years (56–91 years). There were 201 women (91%) included in the study. Baseline patient characteristics are summarized in (Table 1). Of these, 45 patients (20%) had a history of previous fracture-total knee replacement (10 patients, 4%). In addition, patients had disorders such as rheumatoid arthritis (12 patients, 5%), diabetes mellitus (39 patients, 18%), hypertension (64 patients, 29%), liver cirrhosis (6 patients, 2%), and hypothyroidism (36 patients, 16%). In addition, there were 23 patients (11%) had received prior treatment for osteoporosis, including bisphosphonate (13 patients, 7%), a selective estrogen receptor modulator (4 patients, 2%), or teriparatide (6 patients, 2.4%).

Baseline serum albumin, calcium, and alkaline levels were normal. The PTH value was elevated in 114 (57%) patients, significantly elevated in the group that developed hypocalcemia (9.9 vs. 7.6, P: 0.005). Phosphate was reportedly severely low in 8 cases (4%), requiring parenteral correction and normal calcium levels.

Normal or mild renal dysfunction (eGFR: > 60 mL/min/1.73 m2) was noticed in 150 patients (75%), whereas 51 patients (25%) had moderate kidney dysfunction.

None of the patients had hypocalcemia at baseline, but 46 (23%) developed hypocalcemia following a single subcutaneous dose 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 hypocalcemia were mildly asymptomatic ≥ 1.8 mmol/L), and fourteen (30.4%) were symptomatic and required parenteral therapy (< 1.8 mmol/L).

Table 1: Baseline characteristics of patients with and without denosumab-induced hypocalcemia.

	Normal calcium (N 156)	Hypocalcemia N 46	*p* value
Age	60.7±7.9	55.8±8.1	0.968
DM	30	10	
Hypertension	57	20	
Ischemic heart disease	44	14	
Osteoporosis			
Bisphosphonate, n (%)	12 (19.0)	2 (9.1)	0.278
Calcium (mmol/L)	2.37	1.8	0.001
Albumin (gm/L)	35	35	
Alkaline phosphatase (U/L)	288.3±110.6	278.4±102.1	0.702
PTH (pmol/L)	7.6	9.9	0.005
eGFR (mL/min/1.73 m2)	71.4±15.4	67.6±18.0	0.389
Vitamin D (ng/mL)	60.9	59.4	
Phosphate (mmol/L)	1.3	1.2	0.2
Day on which blood sample was drawn after administration of denosumab (median day [IQR])			
1–2 weeks	7.0 (7.0–7.0)	7.0 (7.0–7.0)	0.737
1 month	28.0 (28.0–28.0)	28.0 (28.0–32.0)	0.084

eGFR: estimated glomerular filtration rate; IQR: interquartile range.

Hypocalcemia was corrected temporarily in patients with asymptomatic hypocalcemia with oral calcium supplementations (1,000–3,000 mg/daily). All hypocalcemia patients had elevated PTH.

DISCUSSION

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.[5] The secondary causes for hyperparathyroidism should be excluded, e.g., chronic kidney disease, decreased calcium intake, malabsorption, Vitamin D deficiency, bariatric surgery, renal calcium loss, and certain medications (loop diuretics, bisphosphonates and denosumab).[5] 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.[5,6]

The evaluation of patients who may receive denosumab is the same as recommended for all patients with osteoporosis, e.g., complete blood count, complete chemistry profile (including alkaline phosphatase), calcium, phosphorus, and 25-hydroxyvitamin D.[7] 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.[7] Recently, osteoporosis and metabolic bone disease clinics have been proactively evaluating potential bony defects in patients at risk of high bone turnover from metastatic bone disease or secondary hyperparathyroidism, and normocalcemic hyperparathyroidism conditions have been detected.[8,9]

Denosumab-induced hypocalcemia has been reported in several studies on different diseases. The incidence of denosumab-associated hypocalcemia was 14% (95% CI 9.1–20.7) within six months of treatment despite the widespread use of appropriate calcium/cholecalciferol supplementation.[10] Stages 4 and 5 CKD and male sex were associated with subsequent hypocalcemia.[10] In the FREEDOM trial, hypocalcemia was reported as an adverse event in 1.7% of the denosumab group. More women taking denosumab were reported to have a calcium concentration below 8.5 mg/dL than women in the placebo group at the one-month assessment (1.7% versus 0.4%),[2] reflecting the acute effect of denosumab on osteoclast functionality. Our study showed that the incidence of hypocalcemia was higher, which may be related to low parathyroid hormone levels. A retrospective analysis 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 albumin-adjusted serum calcium and creatinine were the strongest predictors of hypocalcemia. The

hypocalcemia rate increased in strong correlation with a decrease in eGFR.[11]

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 one year,[12] which was in keeping with other results.[13] However, in another prospective study, hypophosphatemia was observed in seven patients among 31 women with osteoporosis.[14] Our study showed 8 cases, and 3 of them required parenteral correction.

The proposed mechanism for developing denosumab-induced hypocalcemia inhibits osteoclastic bone resorption, leading to hypocalcemia by reducing 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.[15] Hypocalcemia is associated with a compensatory PTH elevation. Impairment of the increase in PTH or resistance to PTH action at the level of bone and kidney in patients with CKD may lead to hypocalcemia.[16]

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 one calcium measurement was obtained (the lowest value) in each predefined period; therefore, we could not assess the course of hypocalcemia through a certain period.

CONCLUSION

In conclusion, Denosumab-associated hypocalcemia is more prevalent than previously shown in patients with osteoporosis with adequate calcium and Vitamin D supplementation. In addition, hyperparathyroidism is an important predictive factor in patients with normal calcium and Vitamin D levels.

ACKNOWLEDGEMENT

The authors are grateful for the suggestions and comments from the management of Ahmadi Hospital that have substantially contributed to the final shape of the paper.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

RANKL: Nuclear Factor-κB Ligand; **TNF:** Tumor Necrosis Factor; **PTH:** Parathyroid Hormone; **HPT:** Hyperparathyroidism.

AUTHORS' CONTRIBUTIONS

Z Bitar wrote the article, and A Hajiah collected the data; O Madraani, Jawher, M Zoairi, and Abdul Fatah shared in the discussion and revision of the manuscript. Z Bitar performed the statistical analyses.

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Cite this article: Bita ZI, Hajjiah AMA, Maadarani OS, Elzoueiry MM, Gohar MR, Abdelfatah M, *et al*. Denosumab-induced Hypocalcemia in Patients with Osteoporosis and Normal Renal Function. Int. J. Pharm. Investigation. 2023;13(4):789-92.