Author/s:
Lau, LH;Cliff, ERS;Wong, V;Wong, H;Torkamani, N;Eer, A;Weickhardt, A;Grossmann, M

Title:
Hypocalcaemia following denosumab in prostate cancer: A clinical review

Date:
2020-06-01

Citation:
Lau, L. H., Cliff, E. R. S., Wong, V., Wong, H., Torkamani, N., Eer, A., Weickhardt, A. & Grossmann, M. (2020). Hypocalcaemia following denosumab in prostate cancer: A clinical review. Clinical Endocrinology, 92 (6), pp.495-502. https://doi.org/10.1111/cen.14169.

Persistent Link:
https://hdl.handle.net/11343/275418

DR LIK-HUI LAU (Orcid ID : 0000-0002-9323-5655)

DR MATHIS GROSSMANN (Orcid ID : 0000-0001-8261-3457)

Article type : 5 Unsolicited Review

Hypocalcaemia following denosumab in prostate cancer: a clinical review

Short title: Hypocalcaemia after denosumab in prostate cancer

Lik-Hui Lau[1], Edward R.S. Cliff[2], Vanessa Wong[3], Henry Wong[1], Niloufar Torkamani[1], Audrey Eer[1], Andrew Weickhardt[3], Mathis Grossmann[1,4]

[1]Department of Endocrinology, Austin Health, Melbourne, Australia
[2]Royal Melbourne Hospital, Melbourne Australia
[3]Department of Oncology, Austin Health, Melbourne, Australia
[4]Department of Medicine-Austin Health, The University of Melbourne, Melbourne, Australia

Word Count: Summary 249; Main text 2,673; Table 1, Figure 1.
Supplementary Material: Tables 1, Figures 3.

Correspondence: Dr Mathis Grossmann
Department of Medicine, Austin Health, University of Melbourne, 145 Studley Road, Heidelberg, VIC 3084, Australia
Email mathisg@unimelb.edu.au

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cen.14169

Disclosures: Lik-Hui Lau, Edward Cliff, Vanessa Wong, Henry Wong, Niloufar Torkamani, Audrey Eer, Andrew Weickhardt and Mathis Grossmann declare that they have no conflict of interest relevant to this article.

Summary

Objective: Denosumab is often used in men with advanced prostate cancer to prevent skeletal related events, but can be associated with severe hypocalcaemia. Our objective was to review the pathophysiology, identify risk factors and provide recommendations for prevention and management of denosumab-associated hypocalcaemia.

Design: We reviewed the literature regarding denosumab-associated severe hypocalcaemia, defined as necessitating hospitalization for intravenous calcium treatment, in the context of prostate cancer.

Results: We identified 20 men with prostate cancer with severe denosumab-associated hypocalcemia, including the present case. Median age (range) was 70years (45-86). All had skeletal metastases and presented with symptomatic hypocalcemia 16 days (4-35) after the initial (n=18) or second (n=2) denosumab treatment, with a serum total calcium of 1.36mmol/L (1.13-1.91). The key risk factor was presence of active osteoblastic metastases, evidenced by elevated serum alkaline phosphatase, 838U/L (58-2,620) and supportive imaging. Other risk factors reported in some men included vitamin D deficiency (<50nmol/L), 25-OH vitamin D 44nmol/L (22-81), renal impairment, serum creatinine 103µmol/L (62-1,131), and hypomagnesaemia, 0.82mmol/L (0.29-1.20). Men received intravenous calcium infusions for 16 days (1-90), and median total intravenous elemental calcium requirements were 3.17g (0.47-26.65).

Conclusions: Denosumab treatment in men with metastatic prostate cancer can be associated with life-threatening hypocalcaemia requiring prolonged hospitalization for intravenous calcium treatment. Modifiable risk factors should be corrected before denosumab administration. In men with active osteoblastic metastases, consideration should be given to delay denosumab treatment until underlying disease activity is controlled, and/or be administered with close monitoring and proactive treatment with calcium and calcitriol.

Keywords: Hypocalcaemia, prostate cancer, denosumab, consumption hypocalcaemia, risk factors, pathophysiology, treatment

Introduction

Prostate cancer is the second most common cancer and the fifth leading cause of mortality among men worldwide[1]. Skeletal metastases are common in advanced disease[2] and can result in skeletal-related events (SRE) such as pathologic fractures, spinal cord compression and pain necessitating radiotherapy or surgery to bone. Treatment with denosumab, a receptor activator of nuclear factor-kappa β ligand (RANKL) inhibitor, reduces SRE in men with castrate-resistant prostate cancer[3]. At standard doses, denosumab is more effective than zoledronic acid[4], with a lower SRE incidence (risk ratio 0.84) and a delayed onset to first SRE (risk ratio 0.83) reported in a systematic review[3]. The oncologic benefit of denosumab is considered to be due to its more potent suppression of bone remodeling compared to zoledronic acid[3,5,6], but this may also contribute to an increased risk of hypocalcaemia[7]. Multiple phase 3 randomised clinical trials (RCT) trials comparing treatment with oncologic dosing zoledronic acid (4mg monthly) to denosumab (120 mg monthly) in prostate cancer and other solid organ malignancies have reported a higher risk of Common Terminology Criteria for Adverse Events (CTCAE) all-grade hypocalcaemia (serum calcium <2.1mmol/L) with denosumab (9.6 – 13%) compared to zoledronic acid (3.9 – 6%)[3,4,7-9]. The incidence of all-grade hypocalcaemia was higher (14 – 39.6%) in observational studies[10-12]. Median time to hypocalcaemia was 3.8 months after denosumab compared to 6.5 months with zoledronic acid in RCTs[8]. In observational studies, hypocalcaemia following denosumab occurred between 7 and 25 days[10,13,14] and almost all episodes occurred within the first 6 months[9]. Patients with prostate cancer had a higher recurrence rate of hypocalcaemia with repeated denosumab administration compared to other solid organ malignancies[8]. Most cases of hypocalcaemia reported in these studies were mild and did not require intensive calcium replacement. Severe denosumab-associated hypocalcaemia is, by comparison, relatively uncommon but can be life-threatening.

In this article, we review the existing literature regarding severe denosumab-associated hypocalcaemia, defined as necessitating hospitalisation for intravenous calcium treatment, in the context of prostate cancer. We explore the underlying pathophysiology, identify risk factors and provide recommendations for prevention and management.

PubMed and MEDLINE database searches were conducted to January 2020 using the terms "hypocalcemia", "denosumab", "prostate cancer", "risk factors", "management". The search was supplemented by manual review of references listed within retrieved articles.

Results

Index case

We encountered an unusually severe case of denosumab-induced hypocalcaemia in a 59-year-old man with recently diagnosed bone-metastatic prostate cancer necessitating a prolonged hospital admission with ongoing intravenous calcium requirement despite high dose oral treatment with calcitriol, vitamin D (as cholecalciferol) and calcium supplementation. The case was notable for a unique combination of risk factors, foremost extensive osteoblastic metastases evidenced by suggestive FDG-PET skeletal imaging (**Supplementary Figure 1**), elevated bone density in the spine by DXA, T-score +4.4, and marked elevations in baseline alkaline phosphatase (ALP), 1,348 IU/L [normal range 30-110], and in procollagen type 1 N propeptide (P1NP), >1200 mcg/L [15-80], with pre-existing borderline hypocalcaemia (total calcium 2.01 mmol/L, albumin-adjusted calcium 2.18 nmol/L) (**Supplementary Table 1**). This was compounded by untreated vitamin D deficiency, serum 25 OH-vitamin D 23mol/L, and chemotherapy-related diarrhoea. There was evidence of compensatory secondary hyperparathyroidism (**Supplementary Table 1**). These factors likely contributed to a very early presentation with symptomatic hypocalcemia, serum calcium 1.28 mmol/L, only 4 days after his first denosumab administration (120 mg), with severe clinical features (**Supplementary Figure 2**), compared to a median of 16 days (range 4 to 35) in the entire cohort (**Table 1**). Given his initially uncontrolled skeletal disease activity, requirement for intravenous calcium treatment was prolonged, totaling 25 days, despite concomitant high-dose oral calcium, vitamin D and calcitriol (maximum dose 4 mcg/day) administration (**Supplementary Figure 3)**. The total dose of intravenous calcium administered was 26.65g, the highest reported to date, compared to 0.47 to 7.44 g in previous reports (**Table 1**). His C-terminal telopeptide of type 1 collagen (CTX) level was low-normal on admission, 137 ng/L [normal range 100-600], consistent with rapid denosumab-associated suppression of bone resorption (**Supplementary Table 1**). In contrast, bone formation (a calcium-requiring process), based on the much slower decline in ALP and P1NP (**Supplementary Figure 3)**, remained high for several weeks due to lag in effectiveness of chemotherapy and androgen deprivation therapy, explaining the ongoing large calcium requirements. The reductions in ALP and P1NP, reflecting oncologic control of his skeletal disease confirmed by loss of FDG avidity on PET imaging (**Supplementary Figure 1)**, mirrored the improvement in the hypocalcemia and ultimately allowed weaning and cessation of intravenous calcium treatment (**Supplementary Figure 3)**. As expected, subsequent doses

of denosumab, with concomitant oral calcium and calcitriol treatment, did not cause hypocalcaemia (**Supplementary Figure 3**).

Summary of published case reports of severe denosumab associated hypocalcaemia

We identified 20 published cases (including the previously unpublished index case) of severe denosumab-induced hypocalcaemia in men with prostate cancer, defined as necessitating (as determined by the treating physician) hospitalisation for intravenous calcium administration, corresponding to CTCAE grade 3 and 4 (3=severe, hospitalization needed, 4= life-threatening consequences; urgent intervention indicated), regardless of the serum calcium concentration at presentation. All had skeletal metastases (**Table 1**)[13,15-23]. Eighteen patients were older than 60 years, most had a relatively long history of prostate cancer, and some had received prior bisphosphonate therapy. In the total cohort (n=20), median serum total calcium was 1.36 mmol/L (1.13 to 1.91) at presentation, occurring at a median of 16 days (4-35) after denosumab administration. Ionised calcium, reported in four men, was 0.66 mmol/L (0.58-0.94). Ionised calcium was not reported in the other 16 men (Table 1). Of note, 18 men presented after their first, and two men after their second denosumab dose. ALP levels were elevated, median 838 U/L (58-2,620), as were parathyroid hormone (PTH) levels, median 30.1 pmol/L (12.7- 128.6). Nine of the 20 patients had evidence of evidence of vitamin D insufficiency (25 OH-vitamin D <50 nmol/L), and nine had evidence of renal impairment (increased serum creatinine and/or reduced eGFR). Requirements for intravenous calcium treatment were prolonged in some patients, with a median duration of 16 days (1-90) (**Table 1**).

Symptoms and signs attributable to hypocalcaemia were present in only seven of the 20 cases, and were restricted to features of neuromuscular irritability (spontaneous muscle cramps/spasms, paraesthesias, and positive Trousseau's sign); two cases presented with nonspecific lethargy/fatigue; no seizures were reported. In the remaining 13 cases, the hypocalcaemia was asymptomatic/incidental. In seven of the nine men with available electrocardiograms, the corrected QT interval was prolonged at presentation. Evidence of malabsorption and/or diarrhoea was reported in three cases.

Discussion

Pathophysiology of prostate cancer-bone metastatic disease and its relationship with calcium metabolism

Prostate cancer is typically associated with predominantly osteoblastic skeletal metastases[2,24]. Prostate cancer cells residing in the prostate or in the metastasis microenvironment release bone remodeling and growth factors that result in a net increase in bone formation[2,24,25] (**Figure 1**). Extensive osteoblastic activity can lead to consumption hypocalcaemia even in the absence of anti-resorptive treatment, with rates reaching up to 9 – 33% in retrospective studies[26-31]. A compensatory increase in PTH leads to increased bone resorption via osteoclast activation to maintain a low-normal serum calcium[26]. Denosumab, via inhibition of RANKL[32] potently inhibits this compensatory osteoclast activity, leading to an inhibition of calcium release from bone, and consequently to marked hypocalcaemia (**Figure 1**). In the context of osteoblastic metastases, due to discordance between rapid new bone formation and its slow mineralisation, the calcium deficit can be severe, requiring prolonged intravenous calcium administration (**Table 1**), especially in the context of insufficient oncologic skeletal disease control.

Pharmacology of denosumab

Denosumab is metabolised by the reticuloendothelial system[33] and not dependent on renal or hepatic clearance[34,35]. The volume of distribution is approximately 2.6L/66kg body weight[34,35]. Denosumab demonstrates dose-dependent, non-linear pharmacokinetics across a wide range of doses. Pharmacokinetics and pharmacodynamics do not differ across tumour types and are independent of concomitant cancer therapies[36].

While bone remodeling markers are reduced within 24 hours after denosumab administration, the maximum serum drug level is reached in 7 to 21 days and peak osteoclast suppression usually occurs within the first 2 weeks of treatment[36,37]. Effect duration generally increases with increasing dose and frequency[36,37]. Mean half-life is 29 days (range 25-35 days) in patients receiving 4 weekly injections of 120mg denosumab[36]. Steady state is achieved by 6 months in patients receiving 120mg every 4 weeks[38].

Risk factors for developing hypocalcaemia

Increased bone remodeling due to active skeletal disease

High bone remodeling increases the risk of denosumab-associated hypocalcaemia occurring even if dosed for osteoporosis treatment (60 mg 6-monthly) [39,40]. In prostate cancer, elevated

bone remodeling markers reflect the activity of skeletal metastases[31,41], and patients with active osteoblastic metastases are reliant on increased bone resorption to maintain normocalcaemia[39,40] (**Figure 1**). Pre-clinical data have shown that administration of osteoclast inhibitors to ovariectomised monkeys increased calcium absorption by unmineralized osteoid, with consequent reductions serum calcium[42]. Of note, the importance of bone resorption in maintaining serum calcium in men with uncontrolled osteoblastic metastases from prostate cancer was first recognised in the 1980s, when it was reported that even treatment with oestrogen, a weakly anti-resorptive agent, can trigger frank hypocalcaemia [43,44].

In observational studies of men with metastatic prostate cancer, high baseline bone remodeling was consistently associated with a higher incidence and severity, and a more rapid development of denosumab-associated hypocalcaemia [8,10,13,26,45,46] . This suggests that uncontrolled underlying osteoblastic disease activity is a major, and intuitively modifiable risk factor for denosumab-associated hypocalcemia (*see prevention and treatment below*).

Vitamin D deficiency

Vitamin D is required to enhance dietary calcium absorption, calcium mobilisation from bone and calcium reabsorption from the kidney[47]. Vitamin D deficiency leads to a reduction in gastrointestinal calcium absorption by up to 50%[48,49]. Of note, vitamin D deficiency alone can lead to elevations in PTH and increased bone remodelling. Moreover, intestinal malabsorption, reported in three of the 20 patients in this case series, is associated with vitamin deficiency, and can further reduce intestinal calcium absorption. Not surprisingly, vitamin D deficiency is associated with an increased incidence of hypocalcaemia following intravenous bisphosphonates[50] or denosumab in patients with and without skeletal metastases from malignancy[13].

Chronic kidney disease

Chronic kidney disease (CKD, especially stages 4 and 5), poses a significant risk factor for hypocalcaemia through multiple mechanisms including reduction in renal 1α-hydroxylase activity resulting in reduced activation of 25-hydroxyvitamin D to 1,25 di-hydroxyvitamin D, elevated FGF-23-associated suppression of PTH[51], and hyperphosphataemia leading to increased calcium crystallisation[49,52].

Observational studies have reported an increased incidence of hypocalcaemia in patients with CKD receiving denosumab (60mg 6-monthly), up to 42 – 69% in those receiving haemodialysis[37,53-55]. Patients with CKD may also be treated with cinacalcet which can further increase susceptibility to denosumab-associated hypocalcaemia[53,56]

In a post-hoc analysis of three RCTs administering denosumab 120mg monthly for the treatment of skeletal metastases, hypocalcaemia occurred with increasing incidence with reducing renal function[8]. One retrospective study of 22 patients with a creatinine clearance (CrCL) <30mL/min receiving denosumab 120mg monthly for the prevention of SRE in metastatic renal or breast cancer reported a 45% incidence of all-grade hypocalcaemia and a 14% incidence of grade 3 and 4 hypocalcaemia within 6 months of treatment[57] while another study reported that all patients with a CrCl <30mL/min developed grade 2 or worse hypocalcaemia[37].

Although the pharmacokinetics of denosumab are not altered in CKD, caution is advised; the product information of Xgeva® (denosumab 120mg) warns of a higher risk of hypocalcaemia in patients with a CrCl <30mL/min[38]. While the use of calcitriol in the treatment of denosumab-associated hypocalcaemia has been reported in case reports (Table 1), whether hypocalcaemia can be prevented by proactive calcitriol administration has not been systematically studied.

Hypomagnesaemia

Magnesium is important for the synthesis and release of PTH[58], acting as a cofactor to calcium sensing receptors on the parathyroid gland to regulate PTH secretion. Low magnesium levels suppress PTH release and affect PTH action at target organs such as the bone and kidney[59]. Chronic hypomagnesaemia produces a functional state of PTH resistance. Poor nutrition, diarrhoea and diuretics are associated with hypomagnesaemia. In some case reports, hypomagnesaemia has been documented and may have contributed to the development of hypocalcaemia (**Table 1**).

Prior bisphosphonate use

Denosumab is a potent anti-resorptive and can cause further suppression of bone resorption in patients previously treated with bisphosphonates[5,6]. While intuitively, prior antiresorptive treatment could increase the risk of hypocalcaemia, the data on denosumab after

bisphosphonates are inconsistent with some studies reporting an increased risk of hypocalcaemia while others do not[5,13,60]. However, these studies are difficult to interpret due to lack of randomization and lack of accounting for differences in underlying skeletal disease activity.

Prevention of denosumab-associated hypocalcaemia

Disease control

Given that the risk of severe denosumab-associated hypocalcaemia is substantially dependent on the degree of skeletal osteoblastic metastatic activity, non-urgent denosumab treatment should be postponed until skeletal disease is controlled by oncologic therapy (e.g. chemotherapy, androgen deprivation therapy). Following denosumab administration, close proactive monitoring for hypocalcaemia within the first few weeks and empirical calcitriol and calcium supplementation is recommended in at-risk patients.

Correction of other modifiable risk factors

While evidence specific to men with metastatic prostate cancer is not available, pre-existing vitamin D deficiency and hypomagnesaemia should be corrected and renal function should be optimised. The Xvega® product information recommends daily supplementation of at least 500mg calcium and 400 IU vitamin D[38].

The effect of vitamin D and calcium supplementation in preventing denosumab-associated hypocalcaemia are variable with benefit reported in a post hoc analysis[8], while other studies showed no difference[11]. In retrospective studies, 10-14% of patients developed hypocalcaemia despite the prescription of vitamin D and calcium supplementation[12,46]. In these studies however, compliance with vitamin D and calcium supplementation was not rigorously assessed. In men with CKD, addition of calcitriol treatment to vitamin D supplementation may be considered [61].

Treatment of denosumab-associated hypocalcaemia

While guidelines specific to men with prostate cancer are lacking, the European Society of Endocrinology recommends intravenous calcium treatment for patients with serum calcium <1.9mmol/L and/or symptomatic hypocalcaemia [62]. The preferred intravenous calcium is calcium gluconate (10mL [10% solution] = 1g calcium gluconate = 90mg elemental calcium = 4.65mEq). One to two bolus infusions of 10mLs of calcium gluconate followed by a

continuous infusion with rates of up to 0.5 – 2.0mg elemental calcium/kg/hour or ~5 – 10mLs/hour are suggested [49,62,63]. Oral calcium, vitamin D and calcitriol should be administered concurrently. Calcium carbonate and citrate are the two oral calcium of choice as they contain the highest content of elemental calcium[64]. Hypomagnesaemia is treated with intravenous or oral magnesium supplementation in addition to stopping any precipitating drugs[49,65]. This is followed up by frequent monitoring of serum calcium levels and titration of oral therapies.

Future considerations

Denosumab 60mg given 6 monthly to men with non-metastatic prostate cancer increases bone mineral density and reduces vertebral fracture incidence (RR 0.38 vs. placebo), with a <0.1% incidence of hypocalcaemia[66]. However, such men are at lower risk of developing hypocalcaemia compared to those with skeletal metastases. There are currently no trials examining whether lower dose denosumab maintains effectiveness in preventing SRE or is associated with a lower risk of hypocalcaemia, in metastatic prostate cancer. There are no current trials comparing the use of calcitriol treatment to vitamin D supplementation in the prevention of hypocalcaemia in patients with metastatic prostate cancer.

Conclusion

In patients with uncontrolled osteoblastic skeletal metastases from prostate cancer, denosumab treatment, especially after the first dose, can lead to severe, potentially life-threatening hypocalcaemia. In some men, despite the biochemical severity, hypocalcaemia can be asymptomatic, perhaps due to a relatively slow decline in the serum calcium. Prolonged hospitalization due to ongoing requirement of intravenous calcium treatment may be necessary, especially in the context of predisposing risk factors. In patients with extensive osteoblastic metastases, if feasible, denosumab treatment should be avoided until the disease activity is controlled, e.g. by chemotherapy and/or androgen deprivation therapy. Denosumab associated risk of hypocalcaemia is expected to be low, once control of underlying disease activity is achieved, and modifiable risk factors are optimised. However, close proactive monitoring for hypocalcaemia and empirical treatment with calcitriol, vitamin D and calcium supplementation, should be considered in at-risk patients. Future studies assessing the usefulness of calcitriol supplementation, and whether oncologic efficacy can be maintained and hypocalcaemia risk reduced with lower dosed denosumab, and are needed.

Data Sharing Agreement:

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424.
2. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med.* 2004;350(16):1655-1664.
3. Peddi P, Lopez-Olivo MA, Pratt GF, Suarez-Almazor ME. Denosumab in patients with cancer and skeletal metastases: a systematic review and meta-analysis. *Cancer Treat Rev.* 2013;39(1):97-104.
4. Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. *Eur J Cancer.* 2012;48(16):3082-3092.
5. Body JJ, Lipton A, Gralow J, et al. Effects of denosumab in patients with bone metastases with and without previous bisphosphonate exposure. *J Bone Miner Res.* 2010;25(3):440-446.
6. Morony S, Warmington K, Adamu S, et al. The inhibition of RANKL causes greater suppression of bone resorption and hypercalcemia compared with bisphosphonates in two models of humoral hypercalcemia of malignancy. *Endocrinology.* 2005;146(8):3235-3243.
7. Qi WX, Lin F, He AN, Tang LN, Shen Z, Yao Y. Incidence and risk of denosumab-related hypocalcemia in cancer patients: a systematic review and pooled analysis of randomized controlled studies. *Curr Med Res Opin.* 2013;29(9):1067-1073.
8. Body JJ, Bone HG, de Boer RH, et al. Hypocalcaemia in patients with metastatic bone disease treated with denosumab. *Eur J Cancer.* 2015;51(13):1812-1821.

9. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet.* 2011;377(9768):813-822.
10. Koguchi D, Satoh T, Tsumura H, et al. Risk Factors for Hypocalcemia following Treatment with Denosumab in Patients with Bone Metastases from Prostate Cancer. *Journal of Clinical Trials.* 2016;06.
11. Yerram P, Kansagra S, Abdelghany O. Incidence of hypocalcemia in patients receiving denosumab for prevention of skeletal-related events in bone metastasis. *J Oncol Pharm Pract.* 2017;23(3):179-184.
12. Huynh AL, Baker ST, Stewardson AJ, Johnson DF. Denosumab-associated hypocalcaemia: incidence, severity and patient characteristics in a tertiary hospital setting. *Pharmacoepidemiol Drug Saf.* 2016;25(11):1274-1278.
13. Autio KA, Farooki A, Glezerman IG, et al. Severe Hypocalcemia Associated With Denosumab in Metastatic Castration-Resistant Prostate Cancer: Risk Factors and Precautions for Treating Physicians. *Clin Genitourin Cancer.* 2015;13(4):e305-e309.
14. Lechner B, DeAngelis C, Jamal N, et al. The effects of denosumab on calcium profiles in advanced cancer patients with bone metastases. *Support Care Cancer.* 2014;22(7):1765-1771.
15. Laskowski LK, Goldfarb DS, Howland MA, Kavcsak K, Lugassy DM, Smith SW. A RANKL Wrinkle: Denosumab-Induced Hypocalcemia. *J Med Toxicol.* 2016;12(3):305-308.
16. Muqeet Adnan M, Bhutta U, Iqbal T, AbdulMujeeb S, Haragsim L, Amer S. Severe Hypocalcemia due to Denosumab in Metastatic Prostate Cancer. *Case reports in nephrology.* 2014;2014:565393.
17. Milat F, Goh S, Gani LU, et al. Prolonged hypocalcemia following denosumab therapy in metastatic hormone refractory prostate cancer. *Bone.* 2013;55(2):305-308.
18. Marlow CF, Sharma S, Babar F, Lin J. Severe Hypocalcemia and Hypomagnesemia with Denosumab in Advanced Chronic Kidney Disease: Case Report and Literature Review. *Case reports in oncological medicine.* 2018;2018:2059364.
19. Ali N, Farhat S. Severe Refractory Hypocalcemia in a Patient with Metastatic Prostate Carcinoma Following Denosumab Injection. *Journal of Clinical Case Reports.* 2016;6.
20. McCaleb RV, Johnson JT. SEVERE, PROLONGED, DENOSUMAB-INDUCED HYPOCALCEMIA WITH RECOVERY AFTER 111 DAYS OF HIGH-DOSE

CALCIUM SUPPLEMENTATION. *AACE Clinical Case Reports.* 2019;5(1):e82-e85.

21. Watthanasuntorn K, Abid H, Gnanajothy R. Severe hypocalcaemia following denosumab in a patient with cancer with vitamin D deficiency. *BMJ Case Rep.* 2018;11(1).
22. Pittman K, Antill YC, Goldrick A, Goh J, de Boer RH. Denosumab: Prevention and management of hypocalcemia, osteonecrosis of the jaw and atypical fractures. *Asia Pac J Clin Oncol.* 2017;13(4):266-276.
23. Gunawan F, George E, Kotowicz M. Denosumab-induced hypocalcaemia in metastatic castrate-resistant prostate cancer. *Endocrinol Diabetes Metab Case Rep.* 2019;2019.
24. Abrahamsson P-A. Pathophysiology of Bone Metastases in Prostate Cancer. *European Urology Supplements.* 2004;3(5):3-9.
25. Sohail A, Sherin L, Butt SI, et al. Role of key players in paradigm shifts of prostate cancer bone metastasis. *Cancer Manag Res.* 2018;10:1619-1626.
26. Murray RM, Grill V, Crinis N, Ho PW, Davison J, Pitt P. Hypocalcemic and normocalcemic hyperparathyroidism in patients with advanced prostatic cancer. *J Clin Endocrinol Metab.* 2001;86(9):4133-4138.
27. Tucci M, Mosca A, Lamanna G, et al. Prognostic significance of disordered calcium metabolism in hormone-refractory prostate cancer patients with metastatic bone disease. *Prostate Cancer Prostatic Dis.* 2009;12(1):94-99.
28. Kukreja SC, Shanmugam A, Lad TE. Hypocalcemia in patients with prostate cancer. *Calcif Tissue Int.* 1988;43(6):340-345.
29. Rizzo C, Vella S, Cachia MJ. Refractory hypocalcaemia complicating metastatic prostatic carcinoma. *BMJ Case Rep.* 2015;2015.
30. Fokkema MI, de Heide LJ, van Schelven WD, Hamdy NA. Severe hypocalcaemia associated with extensive osteoblastic metastases in a patient with prostate cancer. *Neth J Med.* 2005;63(1):34-37.
31. Berruti A, Dogliotti L, Bitossi R, et al. Incidence of skeletal complications in patients with bone metastatic prostate cancer and hormone refractory disease: predictive role of bone resorption and formation markers evaluated at baseline. *J Urol.* 2000;164(4):1248-1253.
32. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature.* 2003;423(6937):337-342.

33. Tabrizi MA, Tseng CM, Roskos LK. Elimination mechanisms of therapeutic monoclonal antibodies. *Drug discovery today.* 2006;11(1-2):81-88.
34. Tat SK, Padrines M, Theoleyre S, et al. OPG/membranous--RANKL complex is internalized via the clathrin pathway before a lysosomal and a proteasomal degradation. *Bone.* 2006;39(4):706-715.
35. Keizer RJ, Huitema AD, Schellens JH, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clin Pharmacokinet.* 2010;49(8):493-507.
36. Sohn W, Simiens MA, Jaeger K, Hutton S, Jang G. The pharmacokinetics and pharmacodynamics of denosumab in patients with advanced solid tumours and bone metastases: a systematic review. *Br J Clin Pharmacol.* 2014;78(3):477-487.
37. Ikesue H, Tsuji T, Hata K, et al. Time Course of Calcium Concentrations and Risk Factors for Hypocalcemia in Patients Receiving Denosumab for the Treatment of Bone Metastases From Cancer. *Ann Pharmacother.* 2014;48(9):1159-1165.
38. Amgen Incorporated. XGEVA (denosumab) injection, for subcutaneous use: US prescribing information [online]. Thousand Oaks, CA: Amgen Inc; 2010. http://pi.amgen.com/united_states/xgeva/xgeva_pi.pdf.
39. Ishikawa K, Nagai T, Sakamoto K, et al. High bone turnover elevates the risk of denosumab-induced hypocalcemia in women with postmenopausal osteoporosis. *Ther Clin Risk Manag.* 2016;12:1831-1840.
40. Ishikawa K, Nagai T, Tsuchiya K, et al. High bone turnover status as a risk factor in symptomatic hypocalcemia following denosumab treatment in a male patient with osteoporosis. *Clin Interv Aging.* 2018;13:1929-1934.
41. Jung K, Lein M, Stephan C, et al. Comparison of 10 serum bone turnover markers in prostate carcinoma patients with bone metastatic spread: diagnostic and prognostic implications. *Int J Cancer.* 2004;111(5):783-791.
42. Kostenuik PJ, Smith SY, Samadfam R, Jolette J, Zhou L, Ominsky MS. Effects of denosumab, alendronate, or denosumab following alendronate on bone turnover, calcium homeostasis, bone mass and bone strength in ovariectomized cynomolgus monkeys. *J Bone Miner Res.* 2015;30(4):657-669.
43. Harley HA, Mason R, Phillips PJ. Profound hypocalcaemia associated with oestrogen treatment of carcinoma of the prostate. *Med J Aust.* 1983;2(1):41-42.
44. Vogelgesang SA, McMillin JM. Hypocalcemia associated with estrogen therapy for metastatic adenocarcinoma of the prostate. *J Urol.* 1988;140(5):1025-1027.

45. Kinoshita Y, Arai M, Ito N, et al. High serum ALP level is associated with increased risk of denosumab-related hypocalcemia in patients with bone metastases from solid tumors. *Endocr J.* 2016;63(5):479-484.
46. Imatoh T, Sai K, Takeyama M, et al. Identification of risk factors and development of detection algorithm for denosumab-induced hypocalcaemia. *J Clin Pharm Ther.* 2019;44(1):62-68.
47. DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr.* 2004;80(6 Suppl):1689s-1696s.
48. Holick MF. Vitamin D deficiency. *N Engl J Med.* 2007;357(3):266-281.
49. Tohme JF, Bilezikian JP. Diagnosis and Treatment of Hypocalcemic Emergencies. *The Endocrinologist.* 1996;6(1):10-18.
50. Kohno N, Aogi K, Minami H, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. *J Clin Oncol.* 2005;23(15):3314-3321.
51. Krajisnik T, Bjorklund P, Marsell R, et al. Fibroblast growth factor-23 regulates parathyroid hormone and 1alpha-hydroxylase expression in cultured bovine parathyroid cells. *J Endocrinol.* 2007;195(1):125-131.
52. Md P, Frcp R, PhD T, et al. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism.* 2018:646 - 653.
53. Dave V, Chiang CY, Booth J, Mount PF. Hypocalcemia post denosumab in patients with chronic kidney disease stage 4-5. *Am J Nephrol.* 2015;41(2):129-137.
54. Thongprayoon C, Acharya P, Acharya C, et al. Hypocalcemia and bone mineral density changes following denosumab treatment in end-stage renal disease patients: a meta-analysis of observational studies. *Osteoporos Int.* 2018;29(8):1737-1745.
55. Block GA, Bone HG, Fang L, Lee E, Padhi D. A single-dose study of denosumab in patients with various degrees of renal impairment. *J Bone Miner Res.* 2012;27(7):1471-1479.
56. Bhanot RD, Kaur J, Bhat Z. Severe Hypocalcemia and Dramatic Increase in Parathyroid Hormone after Denosumab in a Dialysis Patient: A Case Report and Review of the Literature. *Case reports in nephrology.* 2019;2019:3027419.
57. Watkins KR, Rogers JE, Atkinson B. Tolerability of denosumab in metastatic solid tumor patients with renal insufficiency. *Support Care Cancer.* 2015;23(6):1657-1662.

58. Anast CS, Winnacker JL, Forte LR, Burns TW. Impaired release of parathyroid hormone in magnesium deficiency. *J Clin Endocrinol Metab.* 1976;42(4):707-717.
59. Rude RK, Oldham SB, Singer FR. Functional hypoparathyroidism and parathyroid hormone end-organ resistance in human magnesium deficiency. *Clin Endocrinol (Oxf).* 1976;5(3):209-224.
60. Stopeck AT, Fizazi K, Body JJ, et al. Safety of long-term denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. *Support Care Cancer.* 2016;24(1):447-455.
61. Buonerba C, Caraglia M, Malgieri S, et al. Calcitriol: a better option than vitamin D in denosumab-treated patients with kidney failure? *Expert Opin Biol Ther.* 2013;13(2):149-151.
62. pitTurner J, Gittoes N, Selby P, Society for Endocrinology Clinical C. SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: Emergency management of acute hypocalcaemia in adult patients. *Endocr Connect.* 2016;5(5):G7-G8.
63. Cooper MS, Gittoes NJL. Diagnosis and management of hypocalcaemia. *BMJ (Clinical research ed).* 2008;336(7656):1298-1302.
64. Harvey JA, Zobitz MM, Pak CY. Dose dependency of calcium absorption: a comparison of calcium carbonate and calcium citrate. *J Bone Miner Res.* 1988;3(3):253-258.
65. Ayuk J, Gittoes NJ. How should hypomagnesaemia be investigated and treated? *Clin Endocrinol (Oxf).* 2011;75(6):743-746.
66. Smith MR, Egerdie B, Hernandez Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med.* 2009;361(8):745-755.

FIGURE LEGEND

Figure 1. Mechanism of hypocalcaemia in metastatic prostate cancer after treatment with denosumab

FGF = fibroblast growth factors, TGF-β = transforming growth factor-β, IGF = insulin-like growth factors, BMP = bone morphogenic proteins, PC3 = prostate cancer cell line, PSA = prostate specific antigen, PTHrP = parathyroid hormone related protein, IL-6 = interleukin-6, RANKL = receptor activator of nuclear factor-kappa β ligand, ALP = alkaline phosphatase, P1NP = Procollagen type 1 N Propeptide, BMD = bone mineral density, CTX = C-terminal telopeptide of type 1 collagen, PTH = parathyroid hormone, Vit D = 25-OH vitamin D

Illustrated are the mechanisms that lead to hypocalcaemia in patients with osteoblastic sekeletal metastases from prostate cancer treated with denosumab. Various growth and resorption factors are released in prostate cancer (red circle). These factors are implicated in causing increased bone remodelling with a net increase in bone formation, evidenced by increased bone mineral density on DEXA in some cases. This leads to calcium requirements for increased bone mineralisation. Untreated vitamin D deficiency reduces gastrointestinal absorption of calcium, and aggravates secondary hyperparathyroidism. Increased PTH stimulates calcium release from bone via osteoclast activation, hence mantaining a low to low normal serum calcium. Anti-resorptives (in yellow) of increasing potency (thicker line represents higher potency) prevent the mobilisation of calcium from bone by inhibiting bone resorption, hence unmasking subclinical consumption hypocalcaemia, and can lead to frank, potentially life-threatening hypocalcaemia.

Table 1: Characteristics of men with metastatic prosate cancer requiring intravenous calcium treatment following denosumab therapy

Characteristic	Median	Range	N
Age (years)	70	45 – 86	20
Ionised calcium (mmol/L)	0.66	0.58 – 0.94	4
Serum total calcium (mmol/L)	1.36	1.13 – 1.91	20
Magnesium (mmol/L)	0.82	0.29 – 1.20	5
Phosphate (mmol/L)	1.1	0.42 – 1.97	8
25-OH Vitamin D (nmol/L)	44	22 – 81	20
PTH (pmol/L)	30.1	12.5 – 128.6	19
Creatinine (µmol/L)	103	62 – 1131	10
eGFR (mL/min/1.73m^2)	66	50 – 90	8
Albumin (g/L)	37	24 – 40	5
ALP (U/L)	838	58 – 2620	16
Total IV elemental calcium requirement (g)	3.17	0.47 – 26.65	8
Time to presentation of hypocalcaemia (days)	16	4 – 35	20
Duration of IV calcium (days)	16	1-90	6
Maximum daily calcitriol dose (mcg/day)	2.0	0.25-32.0	9

PTH = parathyroid hormone, eGFR = estimated glomerular filtration rate, ALP = alkaline phosphatase, IV = intravenous. N represents the number of patients with available results for each parameter. The biochemical parameters reported in the case reports were measured with

site-specific assay methodology used in routine clincal care. Serum total calcium was reported to be albumin-adjusted in 18 cases, whereas in 2 cases, it was not specified whether the serum total calcium was albumin adjusted or not.

Figure 1. Mechanism of hypocalcaemia in metastatic prostate cancer after treatment with denosumab