



# Hypercalcemia upon denosumab withdrawal in primary hyperparathyroidism: a case report and literature review

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## Abstract

Denosumab discontinuation is associated with a rapid increase in bone resorption and a decrease in bone mineral density. Spontaneous vertebral fractures may occur as a side effect of the rebound of bone resorption. Cases of rebound-linked hypercalcemia have also been described, moderate in women with osteoporosis and breast cancer and severe in children receiving oncological doses of denosumab. We report the case of an adult woman with primary hyperparathyroidism and moderate hypercalcemia, treated with denosumab for osteoporosis, who developed severe hypercalcemia and spontaneous vertebral fractures (SVFs) after denosumab discontinuation. An 86-year-old woman with densitometric osteoporosis was treated for 3 years with 60 mg of subcutaneous denosumab every 6 months. She was known to have primary hyperparathyroidism, with a serum albumin-corrected calcium of 2.82 mmol/l (NV 2.15–2.5) at the end of denosumab effect. Nine months after the last denosumab injection, she was hospitalized due to worsening overall health. Clinical evaluation revealed severe hypercalcemia (calcium 3.35 mmol/l). Very high values of bone turnover markers (BTMs) suggested a rebound effect due to denosumab discontinuation. An X-ray showed multiple new SVFs. After injection of denosumab 60 mg, serum calcium rapidly decreased and BTMs were dramatically reduced. A surgical approach by minimally invasive parathyroidectomy allowed for definite resolution of hyperparathyroidism and hypercalcemia. This case suggests that hypercalcemia can be a side consequence of denosumab discontinuation, which can become severe when other causes of hypercalcemia, such as primary hyperparathyroidism, are present.

**Keywords** Bone turnover markers · Case report · Denosumab discontinuation · Hypercalcemia · Hyperparathyroidism · Osteoporosis

## Introduction

Denosumab, a fully human monoclonal antibody that blocks the receptor activator of nuclear factor  $\kappa$ -B ligand (RANKL), is a potent anti-resorptive osteoporosis treatment. Due to its reversible mode of action, bone turnover markers (BTMs) increase rapidly after its discontinuation, accompanied by a quick loss of bone mineral density (BMD) [1]. Spontaneous vertebral fractures (SVFs) have been described in this

situation and a causative link to the rebound of bone resorption has been suggested [2]. Cases of rebound-linked hypercalcemia have also been described after denosumab discontinuation, from completely asymptomatic [3, 4] to severe clinical consequences [5–13]. Only two cases have been described in patients with moderate symptoms treated with denosumab for osteoporosis [4, 14]; all other patients had received denosumab at high (oncological) and/or frequent (minimum every 3 months) dosages.

We report the case of a patient who developed severe acute hypercalcemia after discontinuation of denosumab 60 mg given every 6 months for osteoporosis in the context of known hyperparathyroidism.

## Case report

An 86-year-old woman with hypercalcemia was diagnosed in 2013 in the context of primary hyperparathyroidism by her

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endocrinologist. At that time, she refused the proposed surgical treatment. Due to densitometric osteoporosis (lumbar spine T-score,  $-6.0$  SD; femoral neck T-score,  $-4.5$  SD), denosumab 60 mg was given subcutaneously every 6 months from 2013 to October 2016 (last injection) with good but insufficient effect (04.2015: lumbar spine T-score,  $-5.4$  SD; femoral neck T-score,  $-3.9$  SD). The reason for the treatment discontinuation is unknown. In April 2017, at the end of denosumab efficacy (6 months post last injection), serum albumin-corrected calcium (referred as calcium from here on) level was 2.82 mmol/l (NV 2.15–2.50) and serum parathyroid hormone (PTH) level was 24.2 pmol/l (NV 1.3–9.3) (Table 1). Treatment with cinacalcet 30 mg/day was introduced and calcium decreased to 2.51 mmol/l 1 month later, suggesting good control of hypercalcemia, but the cinacalcet was lowered first and finally discontinued by the patient due

to digestive intolerance. It was reintroduced mid-July 2017 following a re-increase in calcemia (calcium 3.53 mmol/l). At the end of July 2017, the patient was hospitalized due to weight loss (5 kg, 15% body weight), malnutrition, and poor health status (asthenia, confusion). Clinical evaluation revealed severe hypercalcemia (calcium 3.35 mmol/l), with lower PTH under cinacalcet (10.0 pmol/l). The serum 25-OH vitamin D level was 77 nmol/l (NV 50–75). Initial treatment with hydration and intranasal calcitonin only partially corrected calcium to 2.57 mmol/l, and then, despite cinacalcet maintaining low PTH (6.5 pmol/l) calcemia increased again (calcium 3.11 mmol/l). She was at that point referred to our center. Type I collagen c-terminal telopeptide (CTX) was high at 1777 ng/l (NV  $< 573$ ), despite mild renal dysfunction (creatinine 97  $\mu$ mol/l, NV 44–80  $\mu$ mol/l; eGFR 50 ml/min/1.73 m<sup>2</sup>) suggesting a rebound effect due to denosumab discontinuation. A

**Table 1** Treatments and serum analysis results since denosumab introduction until post-parathyroidectomy follow-up

Date	cCa (mmol/l)	PTH (pmol/l)	Creatinine ( $\mu$ mol/l)	CTX (ng/l)/PNP1 ( $\mu$ g/l)	25-OH vit D (nmol/l)	Intervention
30.05.2013	(iCa: 1.43; N 1.15–1.29)				44	Denosumab introduction
10.2016						Denosumab injection
07.04.2017	2.82	24.2*	77		77	6 months after denosumab
05.2017						Cinacalcet 30 mg initiation
30.05.2017	2.51					Cinacalcet reduction to 15 mg
13.07.2017	3.53					Cinacalcet had been discontinued by patient, reintroduction at 30 mg
18.07.2017	3.11	10				
29.07.2017	3.35		69		162	Hospitalization (calcitonin, i.v. hydration, and cinacalcet 30 mg)
03.08.2017	2.57					Under whole treatment
07.08.2017	2.99	6.5*				Under cinacalcet
18.08.2017	3.11					Under cinacalcet
21.08.2017	3.06	9.2*	111	1777/156		Denosumab injection
14.09.2017	2.79	20.9*	93	122/114		
13.10.2017	2.58	31.7	65			
14.11.2017	2.61	34.4				
20.12.2017	2.62				81	
08.02.2018	2.76	20.5 <sup>#</sup>				Denosumab injection
20.09.2018	2.77	16.8 <sup>#</sup>		367/30	96	Denosumab injection
18.10.2018	2.63					
18.01.2019	2.69		71	40/14		
20.02.2019	2.76	28.7 <sup>#</sup>		30/13	76.7	Parathyroidectomy
21.02.2019	2.44	7.5 <sup>#</sup>				Immediate post-surgery
26.02.2019	2.17	18.3*		40/9		
18.03.2019	2.36	4.45 <sup>#</sup>	87	27 / 18		Denosumab injection
11.04.2019	2.38					

iCa, ionized calcium; cCa albumin-corrected calcium, normal values: 2.15–2.50 mmol/l; PTH, parathyroid hormone, normal values: 1.3–9.3 pmol/l or \*1.3–6.8 pmol/l, <sup>#</sup> values initially measured in ng/l, converted into pmol/l; creatinine, normal values: 44–80  $\mu$ mol/l; CTX, C-terminal telopeptide of type I collagen, premenopausal women upper limit: 573 ng/l; PINP, procollagen type 1 N-telopeptide, premenopausal women upper limit: 56.3  $\mu$ g/l; 25-OH vit D, 25-OH vitamin D, normal values  $> 75$  nmol/l

spinal X-ray showed three new SVFs. Denosumab treatment was restored, and after a single 60 mg injection, serum calcium rapidly decreased to 2.63 mmol/l. CTX decreased dramatically to 122 ng/l. With the resumption of denosumab injections (60 mg twice a year), calcemia remained stable between 2.60 and 2.80 mmol/l, without any other treatment. PTH levels increased when calcemia was close to normal values. The patient finally accepted surgical treatment for a parathyroid adenoma identified by neck ultrasound and  $^{99m}\text{Tc}$ -MIBI SPECT/CT scintigraphy. Surgery resulted in calcium normalization in the presence of denosumab treatment (Table 1).

## Discussion

This case suggests that, in patients with known hypercalcemia due to primary hyperparathyroidism, high bone remodeling induced by denosumab discontinuation can elicit acute hypercalcemia with severe clinical consequences.

Denosumab discontinuation induces a rebound effect, with BTMs rapidly increasing over baseline values after its discontinuation, a quick loss of BMD, and an increased risk of SVFs. During this period, hypercalcemia has also been recognized as a consequence of high bone resorption, with most cases described in children [3, 5–11, 15]. Affected children were 4 months to 15 years old, received 120 mg of denosumab (or weight-adapted dosage) for 7 to 42 months, and developed hypercalcemia from 7 weeks to 7 months after the last denosumab injection (Table 2). In seven cases, there were dramatic consequences (hospitalization, bone pain, dehydration with renal insufficiency, bradycardia). In order to normalize calcium values, different management strategies were applied, all including hydration and i.v. bisphosphonates (pamidronate, zoledronate), as well as calcitonin, corticosteroids, furosemide, or, in one case, resumption of denosumab [5]. In all cases, multiple treatments, given for up to 4 weeks, were required to control rebound hypercalcemia [4–7, 10–13, 15].

As the first cases were reported in children, it has been suggested that rebound hypercalcemia was linked to increased bone modeling and remodeling during the growing period [10]. However, since 2018, three cases of severe hypercalcemia needing hospitalization (albumin-corrected calcium 3.10 to 3.59 mmol/l) 4–5 months after the last denosumab injection have been published in adults. A 40-year-old man was treated with denosumab 120 mg monthly for 4 years for a giant cell tumor of the bone [7], and two post-menopausal women were treated with an aromatase inhibitor and denosumab 120 mg quarterly for 5 years [12, 13]. Extensive clinical assessment ruled out any other pathology explaining the hypercalcemia. The giant cell tumor of the bone was in remission [7], and in the other cases, hypercalcemia persisted despite correction of the newly diagnosed hyperthyroidism and antiaromatase discontinuation [13]. In all three cases, BTMs were markedly

elevated at the time of hypercalcemia. In one case, bone scintigraphy performed in the oncological setting showed very high whole body bone uptake [12], supporting the hypothesis of excessive bone remodeling at denosumab discontinuation as the cause of hypercalcemia. In these three cases, high doses of denosumab may explain the development of hypercalcemia.

To date, two cases of hypercalcemia have been reported after discontinuation of denosumab 60 mg every 6 months given for osteoporosis [4, 14] without clinical consequences. A 77-year-old woman with multiple risk factors for osteoporosis, including decreased renal function, was hospitalized 6 months after the last denosumab injection due to dehydration secondary to diarrhea [14]. She had hypercalcemia and suppressed PTH and was treated by rehydration; malignancy was ruled out. A 67-year-old woman treated with denosumab for 10 years developed asymptomatic hypercalcemia with suppressed PTH 6 months after the last injection [4]. Bisphosphonates were given after the diagnosis of thoracic SVFs, and serum calcium progressively decreased. Secondary causes of osteoporosis were excluded. The authors hypothesized that hypercalcemia developed due to the long duration of denosumab treatment [4].

Hypercalcemia does not seem to be frequent at denosumab discontinuation, and was excluded in some clinical trials and case series [1, 2]. Calcemia values at denosumab discontinuation are not mentioned in the other published case series nor clinical trials. Hypercalcemia could be transiently present at the onset of the rebound effect in people without other risk factors for hypercalcemia, and may not have been observed, if the serum calcium levels were measured after this transitional period. The described patients may have experienced severe hypercalcemia for reasons related either to the patient or their pathology (baseline remodeling) or to the treatment (denosumab dosage or duration), with some patients accumulating several characteristics. Our patient was treated with denosumab 60 mg twice yearly for osteoporosis for 3 years, so neither denosumab dosage nor treatment duration can be at the origin of the acute aggravation of the hypercalcemia. The calcemia increased despite lower PTH under cinacalcet, in the context of a dramatic increase in bone remodeling, suggesting it was secondary to denosumab discontinuation.

Few data have been published on the use of denosumab in primary hyperparathyroidism. Administration of denosumab induces a transient increase in PTH values secondary to the serum calcium decrease in post-menopausal osteoporotic women with neither renal dysfunction nor primary hyperparathyroidism [18]. Prolongation of denosumab treatment in patients with primary hyperparathyroidism, which implies repeated transient increases in PTH levels, does not seem to have a stimulating effect on the PTH levels [19]. Very recently, a randomized double-blind trial compared denosumab, denosumab plus cinacalcet, or placebo, given for 1 year, in

**Table 2** Summary of reported cases of hypercalcemia after denosumab discontinuation

Number of pat	Reference	Age, sex	Indication	DMAb dose, frequency, duration	Reason for discontinuation	Delay to hypercalcemia diagnosis	Ca/P values	BTMs, PTH, FGF23	Clinical consequences	Hypercalcemia treatment
1	Boyce et al.; J Bone Miner Res.2012;27:1462 [8]	9 years, M	Fibrous dysplasia, expanding lesion	0.9 mg/kg, 1×/month, 7 doses	Femoral fracture, theoretical risk of delayed fracture healing	2 months	4.5 mmol/l; P normal	P1NP >1000 µg/l, CTX ≥ 5000 ng/l, PTH suppressed	5 days vomiting	Rehydration, repeated bisphosphonate (pamidronate), calcitonin
1	Grasemann et al.; J Clin Endocrinol Metab.2013; 98:3121 [9]	8 years, F	Juvenile Paget's disease	0.5 mg/kg, 1×/6 weeks, 2 doses	Improvement clinical condition	7 weeks	Ca 4.07 mmol/l		Polyuria, nausea, constipation	Bisphosphonate (pamidronate)
1	Gossai et al.; Pediatr Blood Cancer.2015; 62:1078 [5]	10 years, F	Metastatic giant cell tumor of bone	120 mg, 4×/month, then 1×/month, 24 months (28 doses)	Decrease in tumor size and improved pain; risk of osteopetrosis	5 m	Ca 4.15 mmol/l; P normal	PTH suppressed	Nausea, vomiting, acute kidney injury	Aggressive hydration, calcitonin, bisphosphonate (pamidronate), corticosteroids, restart DMAB
1	Satsu et al.; J Bone Miner Metab.2016; 34:118 [6]	10 years, M	Unresectable giant cell tumor of bone	120 mg, 1×/month, 14 months (12 doses)	Development of sclerotic changes in the growth plates	4 months	iCa 3.8 mmol/l; iCa 1.68 mmol/l; P 0.77 mmol/l	PTH suppressed (0.2 pmol/l) #	Nausea, fatigue, alkalosis, renal dysfunction, dehydration, sinus bradycardia with normal QTc	Saline hydration, furosemide, corticosteroid, calcitonin, bisphosphonate (zoledronate, 2×)
10	Hoyer-Kuhn et al.; J Musculoskelet Neuronal Interact.2016; 16:24 [3]	5–11 years, 7 M and 3 F	Osteogenesis imperfecta	1 mg/kg, 1×/3 months, 1 years	Primary endpoint of the study	Not specified	iCa 1.4 mmol/l	Osteocalcin and PTH detectable	No clinical significance	
1	Koldkjer Sølling et al.; Osteoporos Int.2016; 27:2383 [4]	67 years, F	Osteoporosis	60 mg, 1×/6 months, 10 years	End of clinical trial (FREEDOM)	6 months	iCa 3.1 mmol/l; iCa 1.64 mmol/l; P 0.94 mmol/l	PTH suppressed (1.6 pmol/l)	No symptoms	Calcium-vit D substitution discontinuation; hyperhydration
1	Boyce; Curr Osteoporos Rep.2017; 15:283 [10]	23 months, M	Osteogenesis imperfecta type VI	1 mg/kg, 1×/month, 12 months	Not specified	2 months	Hypercalcemia (not specified)	Not assessed	Not specified	Bisphosphonate (pamidronate)
3	Uday et al.; J Clin Endocrinol Metab.2018; 103:596 [7]	15 years, M; 14 years, F; 40 years, M	Giant cell tumor of bone	120 mg, 1×/week first month, then 1×/month, 3.6 years, 1.3 years, 4 years respectively	ONI; end of treatment; femoral cortical stress reaction	7 months; 6 months; 5.5 months	cCa 3.1 mmol/l; cCa 3.4 mmol/l; cCa 4.3 mmol/l; P normal	CTX 3070 ng/l, PTH suppressed	Nausea, vomiting, acute kidney injury, bone pain, inferior members paresthesia	Hyperhydration, furosemide, bisphosphonate (pamidronate)
2	Trejo et al.; J Musculoskelet Neuronal Interact. 2018; 18:76 [15]	2.7 years M; 1.9 years M	Osteogenesis imperfecta type VI	1.3 years, 2.6 years respectively	Study protocol	12 weeks; 9 weeks	iCa 1.54 mmol/l; iCa 1.62 mmol/l	PTH suppressed, hypercalcaemia, CTX elevated	Nephrocalcinosis	Bisphosphonate (pamidronate)
1	Tjelum et al.; Ugeskr Laeger.2018; 180(45) [14]	77 years, F	Osteoporosis	60 mg, 1×/6 months, for 2 years	Hypoparathyroid hypercalcemia and renal dysfunction	6 months	Not specified	Hypercalcemia, PTH suppressed	Dehydration, severely impaired kidney function secondary to diarrhea	Rehydration
1	Roux et al.; Bone.2019;	54 years, F	Adjuvant therapy for breast cancer	120 mg, 1×/month for 6 months, then		4 months	cCa 3.1 mmol/l, P 1.3 mmol/l		Polyuro-polydipsic syndrome, asthenia,	Rehydration, bisphosphonate

**Table 2** (continued)

Number of pat	Reference	Age, sex	Indication	DMAb dose, frequency, duration	Reason for discontinuation	Delay to hypercalcaemia diagnosis	Ca/P values	BTMs, PTH, FGF23	Clinical consequences	Hypercalcaemia treatment
1	120:482 [12]		(clinical trial); antiaromatase	quarterly, total 5 years	Absence of bone metastases; end of clinical trial			CTX 669 ng/l, osteocalcin 64 µg/l	severe constipation, diffuse pain in arms	(pamidronate) 1×/month for 3 months
1	Uchida et al.; Endocr J. 2019, doi: 10.1507 [13]	47 years, F	Adjuvant therapy for breast cancer (clinical trial); antiaromatase	120 mg, 1×/month for 6 months, then quarterly, total 5 years	Absence of bone metastases; end of clinical trial	6 months	cCa 3.59 mmol/l, P 1.29 mmol/l	NTX 510 nmol creat, PTH 2.43 pmol/l <sup>#</sup> , FGF-23/4000 pg/ml	Thirst, appetite loss, bilateral ankle pain	Bisphosphonate (zoledronate)
1	Dür et al.; BMC Musculoskelet Disord. 2019 Oct 20; 20(1):456 [16]	7 years, M	Giant cell tumor of bone	60 mg, 1× in day 8 and 15, then 1/4 weeks, 1 year	Improvement of bone growth and healing of the cyst	6 months	Not specified	Not specified	Not specified	Intensive care treatment necessary (not specified)
1	Upfill-Brown et al.; JBMR Plus. 2019; 3:e10210 [11]	10 years, F	Aneurysmal bone cyst	120 mg, 2×/month the first month, then 1×/month, total 15 doses	Excellent clinical and radiological response	5 months	Ca 3.86 mmol/l, iCa 2.0 mmol/l	Not assessed	Severe diffuse abdominal pain, nausea, vomiting	Bisphosphonates, furosemide, calcitonin
4	Chawla et al.; Lancet Oncol. 2019 dec; 20(12):1719 [17]	25–46 years, gender not specified	Giant cell tumor of bone	120 mg, 1× in days 8 and 15, then 1/4 weeks, 6 months	Study protocol	1 months	Not specified	Not specified	Not specified	Not specified
1	Actual case report	86 years, F	Osteoporosis	60 mg, 1×/6 months, 3 years	Unknown	6 months	cCa 3.35 mmol/l, P 0.9 mmol/l	CTX 1777 ng/l, PTH suppressed	Anorexia, acute kidney injury, weight loss, malnutrition, bad health status	Rehydration, cinacalcet, calcitonin, restart DMAB

DMAB, denosumab; P, phosphate, normal values 0.76–1.41 mmol/l; Ca, calcium; cCa, albumin-corrected calcium, normal values: 2.15–2.50 mmol/l; iCa, total calcium; normal values 1.1–1.3 mmol/l; BTMs, bone turnover markers; PTH, parathyroid hormone, normal values 1.3–9.3 pmol/l, # values initially measured in pg/ml, converted into pmol/l; FGF-23, fibroblast growth factor 23, normal values < 50 pg/ml; CTX, C-terminal telopeptide of type I collagen, premenopausal women upper limit: 573 ng/l; P1NP, procollagen type I N-telopeptide, premenopausal women upper limit: 20.3–56.3 µg/l; NTX, urinary N-telopeptide of type I collagen, normal values 14.3–89.0 nmol BCE/nmol creat (nmol bone collagen equivalents/nmol creatinine)

45 patients with primary hyperparathyroidism [20]. Compared with the placebo group, BMD improved in both groups receiving denosumab, despite an increase in PTH that was not controlled by cinacalcet. At the end of the trial, patients were followed for only 4 weeks, so the consequences of discontinuing denosumab were not assessed.

## Conclusions

Hypercalcemia following denosumab discontinuation has been well described in patients receiving high (oncological) or frequent doses; this has been mainly shown in children, but also in adults, as well as in patients treated with osteoporosis doses. While severe hypercalcemia is probably uncommon, in patients with pre-existent hypercalcemia or with an underlying pathology associated to high bone remodeling, severe hypercalcemia may develop with variable delay after the last denosumab injection. Systematic monitoring of serum calcium levels, i.e., before each denosumab injection, may be suggested in the follow-up of at-risk patients. Although denosumab seems to have a beneficial effect on BMD in patients with primary hyperparathyroidism, the risk of hypercalcemia upon its discontinuation should be taken into account before its introduction. In any case, denosumab should not be interrupted without further therapy.

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**Data availability** All data is included in the manuscript.

## Compliance with ethical standards

**Conflicts of interest** None.

**Ethics approval** The study was in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Consent to participate** Not applicable.

**Consent for publication** Written informed consent was obtained from the patient.

**Code availability** Not applicable.

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