

CASE REPORT

Teriparatide-induced Severe Persistent Hypercalcemia in an Osteoporotic Patient: A Case Report and Literature Review

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Received: 2 July 2024

Accepted: 10 December 2024

Abstract

A rare case of severe prolonged persistent Teriparatide-induced hypercalcemia (14.3mg/dL on admission) in an osteoporotic patient after ceasing the Teriparatide is reported. This 67-year-old female was admitted with polyuria, xerostomia, constipation, progressive weakness, and a history of Teriparatide use due to a previous osteoporotic fracture. Her serum calcium, PTH, and vitamin D levels had been normal before starting Teriparatide. Ninety six hours after ceasing the Teriparatide along with rehydration and Calcitonin treatment, the patient's serum calcium levels returned to normal. Severe Teriparatide-induced hypercalcemia does not follow any defined pattern and may persist for days and can usually be controlled through ceasing the Teriparatide, rehydration, and close monitoring of the serum calcium level and symptoms.

Level of evidence: IV

Keywords: Hypercalcemia, Osteoporosis, Teriparatide

Introduction

Osteoporosis is characterized by bone loss and microarchitectural deterioration, potentially leading to osteoporotic fractures.¹⁻⁶ The primary treatment goal is to prevent new bone fractures by increasing or at least preserving bone mass and quality.^{7,8} Anabolic therapy involving Teriparatide, a recombinant human parathyroid hormone (PTH 1-34), can stimulate both bone formation and resorption. Teriparatide exhibits dual time-dependent effects on bone formation and resorption, enhancing the microarchitecture of both trabecular and cortical bone.^{9,10} Intermittent Teriparatide use in osteoporosis directly enhances osteoblast activity and indirectly promotes bone resorption.¹¹

Teriparatide transiently increases the serum calcium, with a maximal effect at approximately 4.2 h (median increase, 0.4 mg/dl or 0.1 mM) followed by a decline to the pre-dose levels before the next Teriparatide dose administered 24 h later.⁷ Here, we present a case of persistent Teriparatide-induced severe hypercalcemia and literature review.

Case presentation

The patient was a 67-year-old woman with polyuria,

xerostomia, constipation, and progressive weakness. She expressed a history of two osteoporotic fractures in the vertebra and femoral neck since six months ago with no documents for osteoporosis before fracture. She had a history of vitamin D [pearl 50000 IU/week for eight weeks], Calcium-D [calcium carbonate 500 mg + 400 IU vitamin D both once daily], and alendronate [70 mg/week] intake after surgery. The patient was also on Losartan (25 mg twice a day) for chronic hypertension.

Two months after starting the Alendronate treatment, the patient had developed pain in the right thigh. She had stopped taking the medicine on her own and gone to his orthopedist after one month due to the persistent pain.

Imaging for pain aggravation in upper right thigh at one month after finishing the Alendronate, had confirmed right intertrochanteric fracture and hence, Alendronate had been switched to subcutaneous Teriparatide 20 µg once daily [CinnoPar - recombinant human PTH (1-34), CinnaGen, IRAN] since four months before admission.

The patient's history of serum calcium levels before and during the hospitalization for severe Teriparatide-induced hypercalcemia is summarized in [Figure 1].

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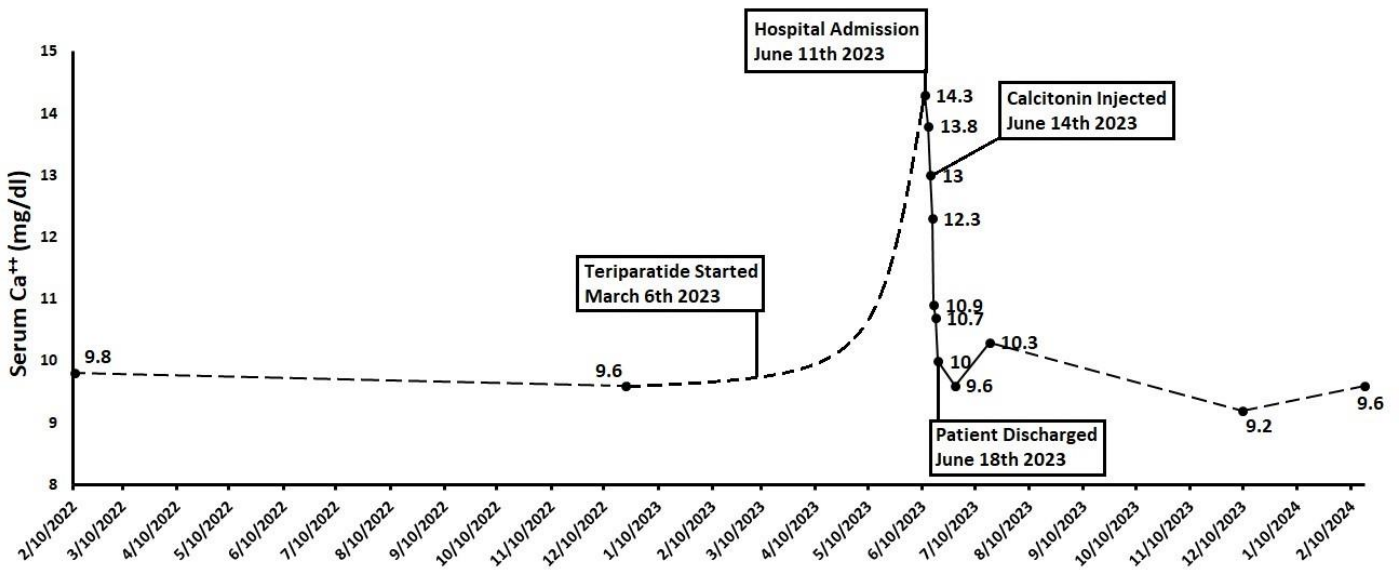


Figure 1. The patient's serum calcium levels before and during hospitalization. The dotted lines indicate uncertain serum calcium levels

Electrocardiography was indicative of a corrected QT interval of 400 msec which is normal [Figure 2].

Apart from the slightly dehydrated mucosa, the patient had stable vital signs and no remarkable problem in physical examination on the admission day. Teriparatide and calcium supplement were ceased and rehydration with saline was

performed. The metabolic panel was also assessed to investigate the possible secondary causes of hypercalcemia, especially malignancy. The serum calcium level was found to be 12.3 mg/dL 40 hours after the last Teriparatide injection, however, it reached below 10 mg/dl 96 hours after admission.

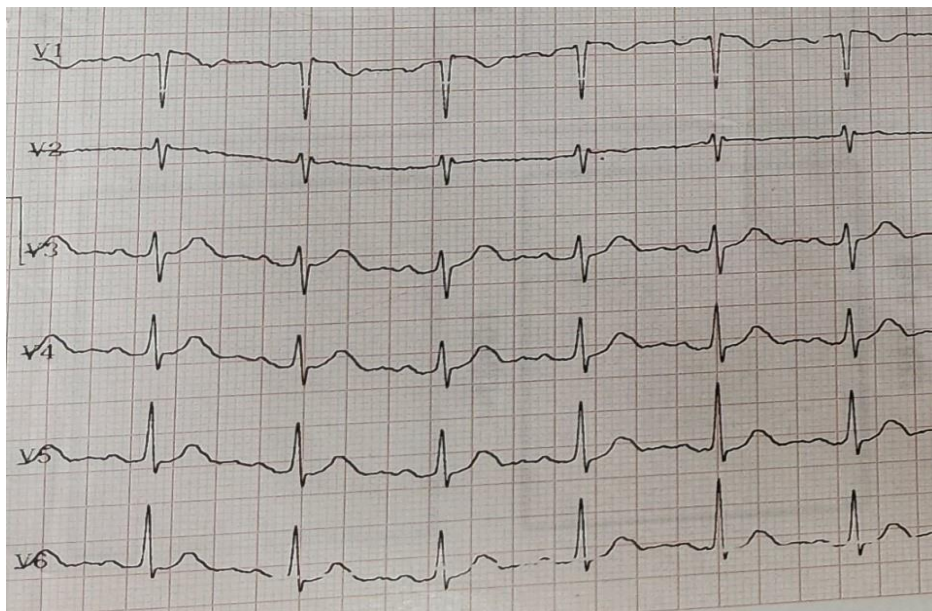


Figure 2. The electrocardiograph taken on admission with Ca⁺⁺=14.3 mg/dL (June 11th)

Dual-energy X-ray absorptiometry (DEXA) was indicative of reduced bone mass, with the following T-score: right femoral neck=-3.1, right total hip=-2.4, and left forearm=-3.3.

The necessary evaluations for a case with hypercalcemia and borderline PTH including the bone density, mammography, serum protein electrophoresis, and chest X-

ray for hypercalcemia-induced malignancy were also performed.

Bilateral mammography showed benign findings (BIRADS 2). No mass lesion or lymphadenopathy were seen in the abdominopelvic, cervical, and parathyroid glands sonography. The skull and chest X-ray as well as serum protein electrophoresis were also normal.

The patient was recovered and discharged four days later.

No hypercalcemia-related symptoms were seen on later follow-ups one, four, and 12 weak after discharge. Her blood chemistry results on various days are shown in [Table 1].

Considering the calcium level in the upper normal range during the patient's follow-up, Denosumab injection was administered to treat the patient's osteoporosis. Three months later, the calcium and PTH levels were checked, and no secondary cause of hypercalcemia was found.

Table 1. The Patient's blood chemistry results on various dates

Parameters (normal values)	3 month before surgery	Before admission	During admission	During admission	Follow up 1	Follow up 2	Follow up 3	Follow up 4
	14 oct 2022 <i>starting Alendronate</i>	7th June	11th June	18th June	28th June	18th July <i>Denosumab injection</i>	9th December	17th February
Hemoglobin (11-14g/dl)	---	---	10.5 (Normal Ferritin)	---	---	---	13.6	---
Magnesium (1.2-2.6mg/dl)	---	---	2	---	---	---	---	---
Calcium (8.5-10.5 mg/dL)	9.8	---	14.3	10.0	9.6	10.3	9.2	9.6
Phosphorus (2.6-5 mg/dl)	3.2	2.7	3.2	3.3	2.8	4.1	4.1	3.9
Vitamin D (30-100 mg/ml)	26	54	---	---	---	57	20	28.3
Parathormone (10- 65 pg/ml)	---	15	21.9	---	---	23	62	32.7
Creatinine (0.1-1.3 mg/dl)	---	1.22	1.3	1	0.9	0.65	0.6	---
Erythrocyte Sedimentation Rate (0-20 mm/h)	---	---	51	---	---	---	24	---
Alkaline phosphatase (64-306U/L)	---	550	---	---	---	---	122	---
24-hour Urine Calcium (40-250 mg/24hr)	---	584	---	---	---	---	---	---

Discussion / Conclusion

Hypercalcemia, with a reported frequency of around 5%, is known to occur even in patients on intermittent Teriparatide therapy.¹² However, the peak serum calcium levels are seen between 4 and 6 h after the drug administration and may remain elevated for 24 h, but return to pretreatment levels by the next day.¹³

Cases of severe persistent Teriparatide-induced hypercalcemia have already been reported with various maximum serum calcium levels and different durations. However, this condition appears to have no specific pattern. Table 2 summarizes seven case reports from different locations. The highest peak of calcium reported was 17.3 mg/dL in a 74-year old Caucasian female from Pennsylvania, USA, with a past medical history of rheumatoid arthritis, Sjogren syndrome, osteoporosis, and multiple joint osteoarthritis, receiving prednisolone, calcitonin, vitamin D, and calcium [Table 2]. In another case reported by Sistla in 2019, immobility, a known

accelerating and exacerbating factor for hypercalcemia, was reported as the sole cause of Teriparatide-induced severe hypercalcemia.¹² It has been emphasized that continuous monitoring of serum calcium levels is necessary during the treatment with Teriparatide in patients with immobility.

Our case of Teriparatide-induced severe persistent hypercalcemia had several unique characteristics:

1. The second highest reported serum calcium level among all previous reports.
2. No remarkable past medical history
3. No history of corticosteroid intake
4. Hypercalcemia persisted up to 96 hours after ceasing the Teriparatide

Considering the severity of hypercalcemia and the persistence of hypercalcemia even 96 hours after the ceasing of Teriparatide injection, the clinical suspicion increased the possibility of underlying causes of

hypercalcemia including primary hyperparathyroidism and hypercalcemia-induced malignancy that was probably exacerbated by Teriparatide. Therefore, despite the initial negative evaluation, the patient was re-examined one month after discharge and then Denosumab was started to

treat osteoporosis.

Teriparatide had been shown to slightly increase the serum calcium and can result in cases of hypercalcemia. Delayed hypercalcemia (continuation of hypercalcemia after 24 hours from the last injection of Teriparatide) is very rare and often asymptomatic and mild.

Table 2. Summary of previous case reports on Teriparatide-induced acute hypercalcemia

Author, year	Location	Case	Past Medical History & Medications	Onset of hypercalcemia	Peak Calcium level (mg/dl)	Duration	Intervention
Cumali Karatoprak, ¹⁵ (2011)	Istanbul, Turkey	74-year old female	<ul style="list-style-type: none"> Osteoporosis, compression fracture Strontium renalate, 	7 months later on Teriparatide	13.6	72 hours	0.9% isotonic saline and furosemide
Nadia Ayasreh, ¹⁶ (2013)	Barcelona, Spain	77-year old male	<ul style="list-style-type: none"> Pacemaker bearer, former smoker, hypertension, dyslipidaemia, hyperuricaemia, severe COPD, ischaemic heart disease, osteoporosis and degenerative osteoarthritis ASA, Allopurinol, Furosemide, Omeprazole, Tramadol, Paracetamol, Simvastatin, Valsartan, Bronchodilators, and NSAIDs 	1 year treatment with Teriparatide	12.9	returned to 10.5 mg/dL after 7 days	Intense fluid replacement + intravenous Furosemide
Maiko Hajime, ¹⁷ (2014)	Fukuoka, Japan	49-year old female	<ul style="list-style-type: none"> Acute intermittent porphyria and glucocorticoid-induced osteoporosis 	2 weeks after treatment with Teriparatide	10.4 (1mg/dL raise from baseline Ca)	-----	Cessation of treatment
Niroshhan Thiruchelvam, ¹⁸ (2014)	Cleveland, USA	65-year old female	<ul style="list-style-type: none"> Steroid dependent COPD, hypothyroidism, severe scoliosis, severe osteoarthritis, and severe osteoporosis levothyroxine, Prednisone, Vitamin D, and Calcium supplement 	5 months after Teriparatide treatment	13.8	48 hours	intravenous fluids, and intravenous pamidronate (30mg)
Divya Systla, ¹⁴ (2019)	Pennsylvania, USA	74-year old female	<ul style="list-style-type: none"> Rheumatoid arthritis, Sjogren syndrome, osteoporosis, compression fractures, multiple joint osteoarthritis. Prednisone, calcitonin, vitamin D, and calcium supplement 	4 months before admission	17.3	3-4 weeks	Intravenous fluids, Intravenous bisphosphonate, and calcitonin
Jovan Milosavljevic, ¹⁹ (2022)	Baltimore, USA	54-year old male 75-year old female	<ul style="list-style-type: none"> Osteoporosis Osteoporosis, diabetes mellitus I, hypothyroidism, hypertension, calciuria, nephrolithiasis Levothyroxine, simvastatin, bupropion, venlafaxine, insulin, dulaglutide, ramipril, fluticasone inhaled, aspirin 	6 months of Teriparatide 6 months into the treatment	11.2 12.5	24 hours Subsequently after hold	Cessation of Teriparatide
Current Study, (2023)	Mashhad, Iran	67-year old female	<ul style="list-style-type: none"> osteoporotic fracture Losartan, Calcium-D and vitamin D supplement 	4 months	14.3	96 hours	Cessation of Teriparatide, Intravenous fluids, SC Calcitonin

Management of hypercalcemia in the studies with PTH analogs is done according to an algorithm. Few strategies that may be effective in preventing hypercalcemia include reducing calcium supplementation and dosage adjustment of Teriparatide from daily to every-other-day administration.²⁰ If hypercalcemia persisted on the repeated analysis, researchers would decrease calcium supplementation to less than 1000 mg daily. If persisting hypercalcemia was found, the dose of PTH analog was reduced by 50%.¹⁷ Therefore, it is recommended that serum calcium should be assessed prior to and after Teriparatide administration.^{20,21}

According to the findings of the current study and review of the previous case reports, although there are several concerns with Teriparatide administration in the treatment of severe osteoporosis:

1. Hypercalcemia seems more likely to happen in elderly patients with upperlimit baseline serum calcium level. This can be attributed to the slower Teriparatide metabolism which needs to be further investigated.
2. Teriparatide-induced acute hypercalcemia does not seem to follow any defined pattern. The duration between starting Teriparatide and onset of hypercalcemia, the peak serum calcium level, and the duration of hypercalcemia after ceasing the Teriparatide are different among various cases.
3. Close monitoring of the calcium level and the warning signs of acute hypercalcemia is recommended.

Acknowledgement

The authors would like to appreciate the help and support from the clinical research development unit, Ghaem hospital, Mashhad University of Medical Sciences, Mashhad, Iran.

Authors Contribution: Authors who conceived and designed the analysis: Ali Moradi, Shokoufeh Bonakdaran/

Authors who collected the data: Sedigheh Reisian/ Authors who contributed data or analysis tools: Mohammad Ali Yaghoubi, Sedigheh Reisian. Ali Moradi/ Authors who performed the analysis: Mohammad Ali Yaghoubi, Sedigheh Reisian. Ali Moradi/ Authors who wrote the paper: Mohammad Ali Yaghoubi, Sedigheh Reisian. Ali Moradi

Declaration of Conflict of Interest: The author(s) do NOT have any potential conflicts of interest for this manuscript.

Declaration of Funding: The authors received NO financial support for the preparation, research, authorship, and publication of this manuscript.

Declaration of Ethical Approval for Study: The ethical approval to conduct this study was provided by the ethics committee of Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.REC.1402.310 On 24/02/2024).

Declaration of Informed Consent: There is no information (names, initials, hospital identification numbers, or photographs) in the submitted manuscript that can be used to identify patients. However, a written informed consent was obtained from the patient (parent or guardian) and is submitted along with the manuscript.

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