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Significant Loss of Areal Bone Mineral Density Following Prolonged Bed Rest During Treatment With Teriparatide

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We present of a case of severe osteoporosis with thoracic myelopathy secondary to nontraumatic T8 compression fracture managed nonsurgically with 3.5 months of bed rest. Despite treatment with teriparatide starting at initial presentation, 1-year follow-up dual energy x-ray absorptiometry scan revealed a significantly greater than expected 19% reduction in lumbar spine bone mineral density (BMD) and a 6% reduction in total hip density. Daily alcohol consumption, severe osteoporosis at baseline, and immobilization secondary to transient myelopathy treated with strict bed rest all likely contributed to unexpected BMD findings.

Freeform/Key Words: teriparatide, osteoporosis, bone mineral density, immobilization

Osteoporosis can result in catastrophic physical, financial, and lifestyle consequences, including severely disabling vertebral compression fracture [1, 2]. Teriparatide, recombinant human parathyroid hormone (1-34) [PTH (1-34)], is US Food and Drug Administration–approved for the following osteoporosis populations at high risk of fracture: men (including hypogonadal men), postmenopausal women, and those with osteoporosis associated with sustained glucocorticoid therapy equivalent to prednisone 5 mg/day or greater [3]. High risk for fracture is defined as history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed with or are intolerant of other available osteoporotic treatments [3]. Bone mineral density (BMD) gain [4–6] and decreased rates of vertebral fracture have been shown in postmenopausal women with teriparatide treatment [1, 5–7]. We report a patient who lost 19% lumbar spine BMD, despite 1 year of teriparatide treatment, in the setting of thoracic myelopathy secondary to nontraumatic T8 compression fracture managed with 3.5 months of bed rest.

1. Case Report

A 79-year-old Caucasian female was referred to the orthopedics clinic with 5 weeks of thoracic back pain, leg paresthesias, and delayed bladder emptying. Body mass index was 22.3 kg/m^2 and Babinski sign was positive bilaterally. Magnetic resonance imaging showed T8 compression fracture with thoracic myelopathy. Dual energy x-ray (DXA) confirmed osteoporosis with lowest T-score of −3.7 at the left femoral neck (Table 1).

Menopause was at age 51 with a 1-year history of hormone replacement therapy. Corticosteroid exposure included intermittent topical treatment of psoriasis (2011) and steroid

Abbreviations: BMD, bone mineral density; DXA, dual energy x-ray absorptiometry; MRI, magnetic resonance imaging; PTH, parathyroid hormone.

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Table 1. DXA Scan Reports Obtained at the Time of T8 Compression Fracture and 1 Year Later

Region	Date	T-Score	BMD	Δ BMD
L1-L4	**9 May 2016**		**0.665**	**−0.168**
	8 May 2015		0.833	
L1, L3, and L4	**9 May 2016**	**-4.6**	**0.621**	**−0.146**
	8 May 2015	−3.4	0.767	
Left femoral neck	**9 May 2016**	**-3.9**	**0.494**	**−0.027**
	8 May 2015	−3.7	0.521	
Left total neck	**9 May 2016**	**-3.7**	**0.538**	**−0.037**
	8 May 2015	−3.4	0.575	
Right femoral neck	**9 May 2016**	**-3.7**	**0.536**	**−0.004**
	8 May 2015	−3.6	0.540	
Right total neck	**9 May 2016**	**-3.8**	**0.528**	**−0.037**
	8 May 2015	−3.5	0.565	
Distal 1/3 radius	**9 May 2016**	**-4.6**	**0.383**	**−0.013**
	8 May 2015	−4.4	0.396	

Boldface text is used to distinguish DXA scan reports obtained 8 May 2015 versus 9 May 2016.

injection into the shoulder and wrist (2013). In 2006, she fell from standing height, followed by chronic upper back pain later diagnosed as vertebral compression fracture requiring T12 kyphoplasty in 2009. Severe acute lower back pain, occurring in the process of being seated, was due to another vertebral compression fracture requiring L2 kyphoplasty in 2015. She was a former 40 pack-year smoker. She had not previously received pharmacologic osteoporosis treatment apart from a calcium and vitamin D supplement of unknown dosage.

Laboratory studies did not show additional causes of osteoporosis (Table 2). Complete blood count, liver function testing, thyroid function testing, and serum protein electrophoresis were also normal.

She was treated with strict bed rest and started on teriparatide in anticipation of surgery. She presented to the endocrinology clinic 3 months later on a gurney, confirming adherence to the bed rest order. After 3.5 months of bed rest deconditioning, she was unable to walk and required an additional 3 months of physical therapy. Active myelopathy had resolved at a 6-month orthopedics follow-up. Because of difficult personal logistics, endocrinology follow-up was not until 1 year later, at which time she was in a thoraco-lumbar-sacral orthosis and had returned to many of her past outdoor activities. There were no new fractures. Body mass index remained stable. She, her family, and pharmacy refill records affirmed compliance with teriparatide and supplemental calcium/vitamin D 600 mg/200 IU twice daily. She reported drinking one to three beers per day. Laboratories showed mild hypercalcemia (Table 2) and 24-hour urine calcium 71 mg/24 hours (0.09 mg/mg creatinine; 1.1 mg/kg body weight). Additional steroid exposure had not occurred. Random morning cortisol was 8.9 mg/dL. Other laboratory values were unremarkable (Table 2). Past imaging showed normal appearing adrenals. A 19% loss in areal lumbar and 6% loss in total hip BMD were found on repeat DXA scan (Fig. 1).

Table 2. Summary of Laboratory Values

Study	Reference Range	May 2015	Aug 2015	May 2016
Calcium	8.5-10 mg/dL	9.2	9.6	10.2
Phosphorous	2.5-4.5 mg/dL		3.3	3
Albumin	3.4-5.0 g/dL	3.7		4.3
Creatinine	0.52-1.04 mg/dL	0.78	0.73	0.84
Parathormone	12-72 pg/mL	29		
Alkaline phosphatase	40-150 U/L	94		114
25-hydroxyvitamin D	20-76 μg/L	57		34

All laboratory values were obtained in the afternoon between 1:00 and 6:00 PM.

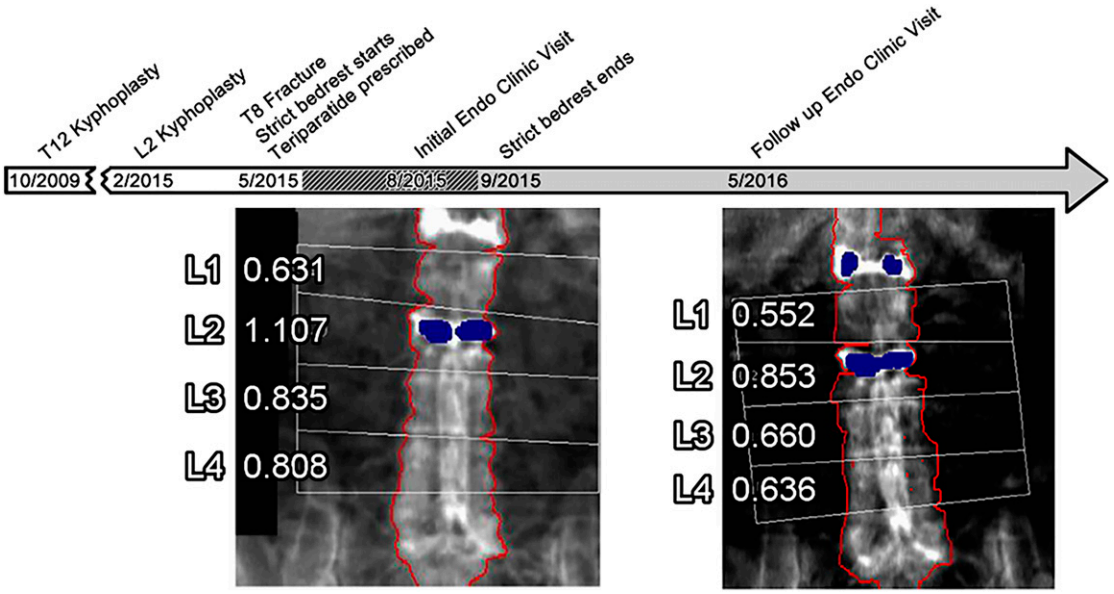

Figure 1. Timeline of major events related to osteoporosis treatment. This includes T12 kyphoplasty, L2 kyphoplasty, endocrine (endo) clinic visits, prescribed bed rest, and lumbar DXA scans demonstrating significant loss in BMD despite treatment with teriparatide over the course of approximately 1 year.

2. Discussion

We present a case of severe, longstanding, and previously untreated osteoporosis with associated 19% loss of lumbar spine BMD during 1 year of teriparatide treatment. Lumbar spine BMD loss is unusual and unexpected in the setting of teriparatide treatment [5, 8]. We hypothesize that immobilization may have decreased and/or reversed the expected BMD gain response to teriparatide.

Immobilization increases bone resorption and bone loss [9]. This has been demonstrated in hospitalized patients [10], those with spinal cord injury [11–13], and healthy subjects subjected to bed rest [14, 15]. However, in these groups, the bone loss has been less than we observed. Specifically, a group of adults lost on average 3.6% (with a range up to 10%) lumbar BMD during short-term bed rest treatment of lumbar intervertebral disc protrusion [10]. Spinal cord injury paralysis has been associated with bone loss below the injury, including up to 4% per month lower limb BMD losses [11], but lumbar spine losses have not been shown [12, 13]. In contrast, healthy individuals on forced bed rest lost an average 2.9% in lumbar spine BMD over 12 weeks [14] and 3.6% over 17 weeks [15]. Adolescent girls lost 15% BMD at the L4 vertebra during 6 weeks of bed rest following operation for scoliosis [16].

The anabolic mechanism and previously reported increases in spine BMD [4–6] made teriparatide an attractive treatment option for our patient. Our patient's very low baseline BMD (lumbar spine 0.62 g/cm^2) may have inflated the unexpected percent BMD loss compared with other studies, where baseline lumbar spine BMD was higher (*i.e.,* 0.81 to 0.82 g/cm^2) [4, 6, 8]. Although radial bone loss can be seen with teriparatide treatment [4–6], axial bone loss is rare. An average −6.2% loss in femoral neck BMD was reported in only 10% of postmenopausal women after 1 year of teriparatide in the Fracture Prevention Trial. However, these same women still gained lumbar spine BMD and had reduced vertebral fracture risk [8]. Heany also reported a low rate of BMD loss at the hip, but not the lumbar spine, in teriparatide-treated subjects [17]. More common than bone loss is nonresponse to teriparatide, with lumbar spine nonresponse rates ranging from 2% to 19% [17–20].

Teriparatide-associated loss of areal BMD at the radius, in contrast to axial sites [4–6], is hypothesized to be due in part to its nonweight-bearing status [21]. We were unable to find other reports of teriparatide use in the treatment of advanced baseline osteoporosis during

prolonged bed rest. PTH (1-34) prevented bone loss in animal studies of limb immobilization [22, 23] and it synergistically increased bone growth when combined with weight-bearing [23, 24]. In contrast, teriparatide plus mechanical loading was not associated with change in axial BMD in spinal cord injury patients [25].

Fracture risk may not correlate with the BMD loss [8]. Increased bone size, with undermineralized osteoid, might be accompanied by teriparatide-associated improvements in strength [5]. Likewise, in the Fracture Prevention Trial, most of the teriparatide-associated fracture risk reduction was attributed to non-BMD determinants of bone strength, with the greatest impact in the lowest quartile of baseline BMD [26]. Indeed, our patient has not had a fracture while on teriparatide treatment.

Other potential causes of BMD loss in this patient, and limitations of our report, merit consideration. Teriparatide compliance was assessed by historical report and the expected therapy-associated increase in serum calcium, but not bone turnover markers. Although her urine calcium was normal (1.1 mg/kg body weight) [27], it was lower than previously reported on teriparatide (mg/day) [28]. Normal baseline PTH and 25-hydroxyvitamin D (Table 2) argue against coexistent hyperparathyroidism. Still, teriparatide has increased BMD even in subjects with low 25-hydroxyvitamin D [29]. Dexamethasone suppression test was not performed. A bone gain response to teriparatide would be expected, based on studies in glucocorticoid-induced osteoporosis [30, 31] if she had subclinical Cushing syndrome. Impaired response to PTH regulation of bone, or osteoblasts [32, 33], could theoretically cause both severe osteoporosis and teriparatide nonresponse. Finally, alcohol decreased the therapeutic efficacy of PTH (1-34) in animal models [34, 35], leaving open the contribution of her alcohol intake to the BMD loss.

This case highlights an unexpected clinical scenario of teriparatide nonresponse, with significant loss of lumbar spine BMD. Alcohol consumption, severe baseline osteoporosis, and immobilization secondary to myelopathy and bed rest all likely contributed to the BMD losses. This unusual case may raise caution against the use of teriparatide in the setting of immobilization.

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