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Case Report

Teriparatide and Bone Turnover and Formation in a Hemodialysis Patient With Low-Turnover Bone Disease: A Case Report

Patricia Palcu,[1] Natalie Dion, PhD,[2] Louis-Georges Ste-Marie, MD,[2] David Goltzman, MD,[3,4] Ina Radziunas, BSN, MEd,[1] Paul D. Miller, MD,[5] and Sophie A. Jamal, MD, PhD[1]

Teriparatide, a recombinant form of parathyroid hormone, is an anabolic agent approved for use in women and men with osteoporosis. However, it is not well studied in people with chronic kidney disease (CKD). We report on a patient with stage 5 CKD treated with dialysis who presented to our clinic with multiple fractures, including bilateral nondisplaced pelvic fractures resulting in chronic pain and interfering with the patient's ability to work. Bone histomorphometry demonstrated low-turnover bone disease, and he was treated with 20 μg of teriparatide (subcutaneous injection) every morning for 24 months. Within 6 months of initiating therapy, the patient's pain resolved and he was able to resume work. Serum calcium and phosphate levels remained within reference ranges throughout his treatment, and he sustained no further fractures. During 24 months of treatment, bone mineral density was maintained at the lumbar spine, and there was an increase of 4% at the femoral neck and total hip. A second transiliac bone biopsy demonstrated improvements in static and dynamic parameters of bone formation. In our patient, 24-month treatment with teriparatide was safe and effective; however, larger studies are needed to determine the efficacy of teriparatide in the dialysis-dependent CKD population.

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Chronic kidney disease (CKD) is associated with an increased risk of fracture. Reduced bone turnover, or adynamic bone disease, is one factor that may contribute to the excess fracture risk.[1] A potential treatment for low-turnover bone disease is teriparatide, a recombinant form of the first 34 amino acids of parathyroid hormone (PTH) that increases osteoblast activity.[2] Teriparatide decreases fracture risk in postmenopausal women with osteoporosis.[3] The use of this agent in CKD is limited to 3 small studies, none of which report the effects of teriparatide on bone histomorphometry.[4-6]

We report on bone mineral density (BMD) and bone histomorphometric responses in a dialysis-dependent patient with stage 5 CKD and low-turnover bone disease treated with teriparatide.

CASE REPORT

A 41-year-old white man was followed up on an intermittent basis in the Multidisciplinary Osteoporosis Program at Women's College Hospital, a tertiary-care center located in downtown Toronto, Canada.

In 1979, the patient developed membranoproliferative glomerulonephritis and initiated peritoneal dialysis therapy. He underwent cadaveric kidney transplantation in 1980, and the transplant failed 2 years later. He received a second cadaveric transplant in 1983, which failed in 1995. He has since received thrice-weekly hemodialysis. In 1998, the patient sustained a wrist fracture after slipping on ice, prompting his initial referral to our clinic.

The patient worked as a dairy farmer. He did not smoke or drink alcohol. His paternal grandmother had a hip fracture.

At the time of initial assessment, the patient's serum calcium level was 2.37 (reference range, 2.10-2.60) mmol/L, phosphate level was 1.92 (reference range, 0.81-1.45) mmol/L, and intact PTH level was 23.5 (reference range, 1.6-7.2) pmol/L. He was treated with vitamin D_3, 1,000 IU, and calcitriol, 0.25 μg, 3 times per week. He was taking calcium carbonate, 500 mg, with lunch and dinner as a phosphate binder.

In 2003, the patient had a hip fracture after a fall and was reassessed in our clinic. Laboratory testing demonstrated elevations in calcium (2.67 mmol/L), phosphate (1.70 mmol/L), alkaline phosphatase (189; reference range, 34-115 IU/L), and intact PTH (27.5 pmol/L) levels. These parameters remained elevated, and he underwent total parathyroidectomy with autotransplantation of one gland to the forearm. He was prescribed calcitriol, 0.5 μg, 3 times per week, and calcium carbonate, 500 mg, with each meal.

From the [1]Division of Endocrinology and Metabolism, University of Toronto and Women's College Research Institute, Toronto; [2]Department of Medicine, Université de Montréal, Bone Histomorphometry Laboratory, Centre Hospitalier de l'Université de Montréal; [3]Department of Medicine, McGill University; [4]Department of Medicine, McGill University Health Centre, Montreal, QC, Canada; and [5]University of Colorado Health Sciences Center and Colorado Center for Bone Research, Lakewood, CO.

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Address correspondence to Sophie A. Jamal, MD, PhD, Women's College Research Institute, 790 Bay St 7th Floor, Toronto, ON, Canada M5G 1N8. E-mail: sophie.jamal@utoronto.ca

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The patient was seen again in March 2010. His primary care physician noted a decrease in BMD by dual-energy x-ray absorptiometry by 6.9% at the spine, 5.8% at the femoral neck, and 6.6% at the total hip from 2009 to 2010. Since his last visit to our clinic in 2003, he had several low-trauma fractures, including bilateral nondisplaced pelvic fractures (identified by bone scintigraphy) causing severe pelvic pain and interfering with his ability to work. He was taking calcium carbonate, 1,000 mg, with each meal; calcitriol, 0.25 μg, weekly; vitamin D_3, 1,000 IU/d; and since January 2010, calcitonin, 100 IU, subcutaneously 3 times a week. Laboratory testing demonstrated the following values: serum calcium, 2.57 mmol/L; phosphate, 1.74 mmol/L; 25-hydroxyvitamin D, 127 (reference range, 75-225) nmol/L; 1,25-dihydroxyvitamin D (1,25 $[OH]_2D$), 10 (reference range, 39-193) pmol/L; alkaline phosphatase, 106 IU/L; and intact PTH, 6.2 pmol/L.

The patient stopped calcitonin and calcitriol treatment and 6 months later underwent a double tetracycline–labeled transiliac bone biopsy. The biopsy specimen showed reduced osteoid volume, osteoblast surfaces, and mineralizing surfaces, with very few sites of double labeling and a low depth of resorption lacunae. Because there was some resorption activity, histomorphometric findings were consistent with hypodynamic low-turnover bone disease (Table 1; Fig 1).

We treated the patient with teriparatide, 20 μg, subcutaneously every morning (or after dialysis on dialysis days) for 24 months. He continued to take calcium and vitamin D_3 as previously prescribed and restarted calcitriol treatment. Within 6 months of initiating teriparatide therapy, the patient's pain resolved and he resumed work. Bone scintigraphy 12 months after initiating therapy indicated that his pelvic fractures had healed. Serum calcium, albumin, and alkaline phosphatase levels remained within reference ranges throughout his treatment. Serum phosphate levels stayed above the reference range, but were not significantly different from pretreatment values (Table S1). The patient sustained no further fractures.

Over 24 months of treatment, BMD was maintained at the lumbar spine, and there was an increase of 4% at the femoral neck and total hip. A second transiliac bone biopsy demonstrated improvements in static and dynamic parameters of bone formation (Table 1; Fig 1). For example, there was a 3.6-fold increase in bone formation rate and a 26% increase in wall thickness.

To evaluate the pharmacokinetic behavior of teriparatide in our patient, we monitored PTH (separately measuring its amino-terminal [amino acids 1-34] and intact [amino acids 1-84] forms), $1,25[OH]_2D$, phosphate, calcium, and albumin levels before and after teriparatide injection. In brief, we took blood samples following a 10-hour fast; administered teriparatide, 20 μg, subcutaneously; and then took blood samples at 15-minute intervals for 1 hour and at 30-minute intervals for an additional 3 hours. Following administration of teriparatide, there was a peak in serum PTH (1-34) level at 30 minutes; serum calcium and phosphate levels remained within the reference ranges throughout the entire monitoring period, and there was no increase in PTH (1-84) or $1,25(OH)_2D$ levels (Fig S1; Table S2).

DISCUSSION

To our knowledge, this case report is the first to demonstrate that in a patient with dialysis-dependent CKD and severe low-turnover bone disease, teriparatide can increase bone remodeling and improve BMD. Ultimately, these effects may help reduce fractures.

Of note, following teriparatide treatment, bone histomorphometric parameters in our patient showed a marked improvement of bone remodeling, including an almost 4-fold increase in the activation frequency. In the post-teriparatide biopsy, stimulation of bone turnover produced a net positive bone balance, as indicated by higher values of the formation period and wall thickness. Our findings are consistent with histomorphometric data in postmenopausal women with osteoporosis, which show an increase from 38.5 to 41.7 μm in wall thickness from baseline to post-teriparatide treatment.[2]

The increase in femoral neck BMD (4%) that we observed in our patient is consistent with data reported in post hoc analyses of the Fracture Prevention Trial: teriparatide treatment increased BMD by ~2.5% among patients with estimated glomerular filtration rates between 30 and 49 mL/min/1.73 m^2.[3] Our BMD

Table 1. Histomorphometric Measurements

Measurements	Pre–Teriparatide Treatment	Post–Teriparatide Treatment
Trabecular volume (BV/TV), %	3.6 (19.5 ± 4.9)[a]	13.8
Osteoid surface (OS/BS), %	11.1 (14.4 ± 5.9)[a]	40.6
Osteoid volume (OV/BV), %	1.5 (2.7 ± 1.3)[a]	8.5
Osteoid thickness (O.Th), μm	7	10
Osteoblast surfaces (Ob.S/BS), %	0.37	1.95
Wall thickness (W.Th), μm	24.3	30.6
Eroded surfaces (ES/BS), %	2.3 (3.6 ± 1.1)[a]	10.8
Osteoclast number (N.Oc/E.Pm), no./mm	0.92	5.47
Mineralizing surface (MS/BS), %	3.3	18.3
Mineral apposition rate (MAR), μm/d	0.96[b] (0.72 ± 0.12)[a]	0.63
Bone formation rate (BFR/BS), $\mu m^3/\mu m^2/y$	11.7	42.2
Mineralization lag time (Mlt), d	24.1	35.5
Osteoid maturation time (Omt), d	7.3	16
Formation period (FP), d	32.4	61.3
Activation frequency (Ac.f), no./y	0.48	1.38

Note: Histomorphometric abbreviations and nomenclature follow the recommendations provided by the American Society for Bone and Mineral Research.[8]

[a]Values in parentheses are reference values for cancellous bone of transiliac bone biopsies for individuals of the same age and sex.[9]

[b]Measured on the very few sites of double labeling.