

Teriparatide treatment in adult hypophosphatasia in a patient exposed to bisphosphonate: a case report

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Summary

We describe the case of a woman with hypophosphatasia previously exposed to bisphosphonate and subsequently treated with teriparatide (recombinant human PTH 1-34).

A Caucasian woman sustained bilateral femur stress fractures when she was fifty years old, which widened despite use of calcium, vitamin D and risedronate for 2.5 years and required intramedullary rods for stabilization. Hypophosphatasia was diagnosed in the interim due to low serum alkaline phosphatase (ALP) (ALP 20 IU/L; normal (N), 40-150 IU/L) and high pyridoxal 5' phosphate (3400 nmol/L; N 18-175 nmol/L). She was referred for further management. On presentation, she had significant fracture site pain and generalized bone pain (weight bearing and non-weight bearing) - making her walker dependent at home and wheel chair dependent outside home. She could not sleep at night due to discomfort when she moved. Daily teriparatide injections, 20 mcg subcutaneously were prescribed.

At 8-weeks follow-up, fracture site pain, weight-bearing and non weight-bearing pain improved significantly allowing ambulation for prolonged periods without assistance. She slept at night without discomfort. Improvement persisted during her entire treatment period. Radiographs taken at 4 and 16 months of treatment demonstrated healing of femur fractures. Biochemically, mean urine cross-link-N-telopeptide increased 11% as compared to her base-line, while bone specific alkaline phosphatase did not increase as expected.

In conclusion, we observed an uncoupling of bone formation and resorption markers during her treatment period in the face of notable clinical and radiological improvement. Off-label use of teriparatide may help patients with hypophosphatasia.

KEY WORDS: osteomalacia, alkaline phosphatase; pyridoxal phosphate.

Abbreviations: ALP= alkaline phosphatase; BMD= bone mineral density; BSALP= Bone specific alkaline phosphatase; DXA= dual-energy x-ray absorptiometry; NTX= cross linked N-telopeptide; PLP= pyridoxal phosphate.

Introduction

Hypophosphatasia (OMIM: adult # 146300; infantile # 241500; childhood # 241510) is a rare inborn error of metabolism biochemically defined by subnormal enzyme activity of tissue non-specific alkaline phosphatase (ALP), which causes defective skeletal and dental mineralization (1). Its clinical presentation is highly variable. It can cause death in utero, rickets in infancy and childhood, and osteomalacia in adults (1). Two other forms are odynohypophosphatasia (dental manifestations only, no skeletal manifestations) and pseudohypophosphatasia (clinical manifestations only, normal ALP levels) (1). Genetically, it is caused by a deactivating mutation of tissue non-specific ALP gene (gene map locus 1p36.1-p34) resulting in an accumulation of its substrates- pyridoxal phosphate (PLP), inorganic pyrophosphate and phosphoethanolamine. Inorganic pyrophosphate acts an inhibitor of skeletal mineralization (1).

There is no established medical treatment for this condition. There have been 2 recent case reports of bisphosphonate naïve adult hypophosphatasia patients treated with teriparatide for 18 and 24 months (2, 3). We report an adult hypophosphatasia patient previously treated with risedronate who clinically and radiographically demonstrated improvement after 34 months of teriparatide treatment.

Case report

A 53-year-old post-menopausal Caucasian woman was referred for management of hypophosphatasia. At age 50 years, she complained of pain in her lower limbs. Radiographs demonstrated bowing, diffuse bone demineralization and bilateral stress fractures in the lateral cortices of both femurs. Base-line dual-energy x-ray absorptiometry (DXA) (GE Lunar, Madison WI) revealed anteroposterior lumbar spine bone mineral density (BMD) of 1.031 g/cm² (T-score -1.4; Z-score -0.3) and total femur BMD of 0.638 g/cm² (T-score -3.0; Z-score -2.1) consistent with osteoporosis. After treatment with calcium, vitamin D and 35 mg weekly dose of risedronate, there was no improvement in fracture site pain. BMD a year later decreased further at the hip with a dual femur density of 0.616 gm/cm² (T-score -3.2; Z-score -2.3) while spine BMD remained stable.

After 2.5 years of risedronate therapy, when patient did not improve clinically and when radiographs showed widening of both femur fractures, this drug was discontinued and intramedullary rods were placed bilaterally. Repeat radiographs 10 months later (and one month prior to presentation) showed incomplete repair of both femur fractures. Hypophosphatasia was diagnosed in the interim due to low serum ALP (20 IU/L; normal (N), 40-150 IU/L) and high serum PLP (3400 nmol/L; N 18-175 nmol/L) levels. She was referred to us for further management. Upon presentation she complained of generalized skeletal pain, both weight-bearing and non weight-bearing. She used a walker at home and wheel chair outside the home. She could not sleep at night due to skeletal discomfort. She reported premature loss of permanent teeth that began in late teens and a seizure disorder that started at age 16 years. This was well controlled on primidone with no occurrence of seizures for >12

years. She also had partial bilateral hearing loss that did not require hearing aids. This did not progress, and remained of unclear etiology as she did not want to pursue further work-up. Menses started at 16 years of age and were regular. She underwent natural menopause in her mid-forties. She did not develop any hot flashes and never used hormone replacement therapy. Her medications included primidone for seizure disorder, vitamin B12 and iron supplements, desloratidine and azelastine nasal spray for seasonal allergies and lorazepam for generalized anxiety disorder. She had 2 healthy teen age boys, actively involved in contact sports and without skeletal problems. Her older sister was diagnosed with low BMD, used alendronate and had not developed any fractures. Her maternal aunt had Paget's disease.

Her base-line biochemical profile is presented in Table I. Her clinical presentation, low serum ALP and high serum PLP levels were diagnostic of hypophosphatasia (1). She was started on daily oral vitamin D (400 IU) and teriparatide injections, 20 mcg subcutaneously.

Results

Within a few weeks of starting teriparatide, our patient's weight-bearing and non weight-bearing bone pain decreased greatly. She ambulated for progressively longer periods of time without support and slept at night without pain. This resulted in a considerable improvement in her psyche. Her spouse concurred with these findings. When she self withheld teriparatide for a month due to subjective dizziness, her pain reappeared and promptly resolved again on restarting treatment. Over the

course of her treatment, she reported several falls without new fractures.

Radiographs performed 10 months after intra-medullary rodding and prior to teriparatide therapy showed incomplete healing of both femur fractures. Radiographs performed at 4 and 16 months of teriparatide treatment demonstrated progressive healing of the fractures (Figure 1). Due to excellent clinical and radiological response, teriparatide was continued. On her last visit (at 34 months of treatment), she ambulated without any support and showed no discomfort on musculoskeletal examination.

The following changes were noted on her biochemistry (Table I): (1) mean calcium, phosphorus, 25 (OH) vitamin D and vitamin B6 remained unchanged (<10% change from baseline), (2) mean PTH decreased 28%, (3) mean 1, 25 (OH) D2 increased 70%, and (4) mean urine cross linked N-telopeptide (NTX) increased 11%. Although we do not have a base-line value for BSALP, it failed to increase as expected on treatment in spite of an increase in urine NTX.

Follow up DXA scans on teriparatide treatment were performed on different machines. Changes were not comparable and therefore have not been reported. Mutation analysis of the TNSALP gene or iliac crest histomorphometry were not performed. Bone scans were not performed as well.

Discussion

Our patient's limiting symptom that affected her quality of life was weight bearing and non-weight bearing bone pain- which promptly and significantly improved with teriparatide. This de-

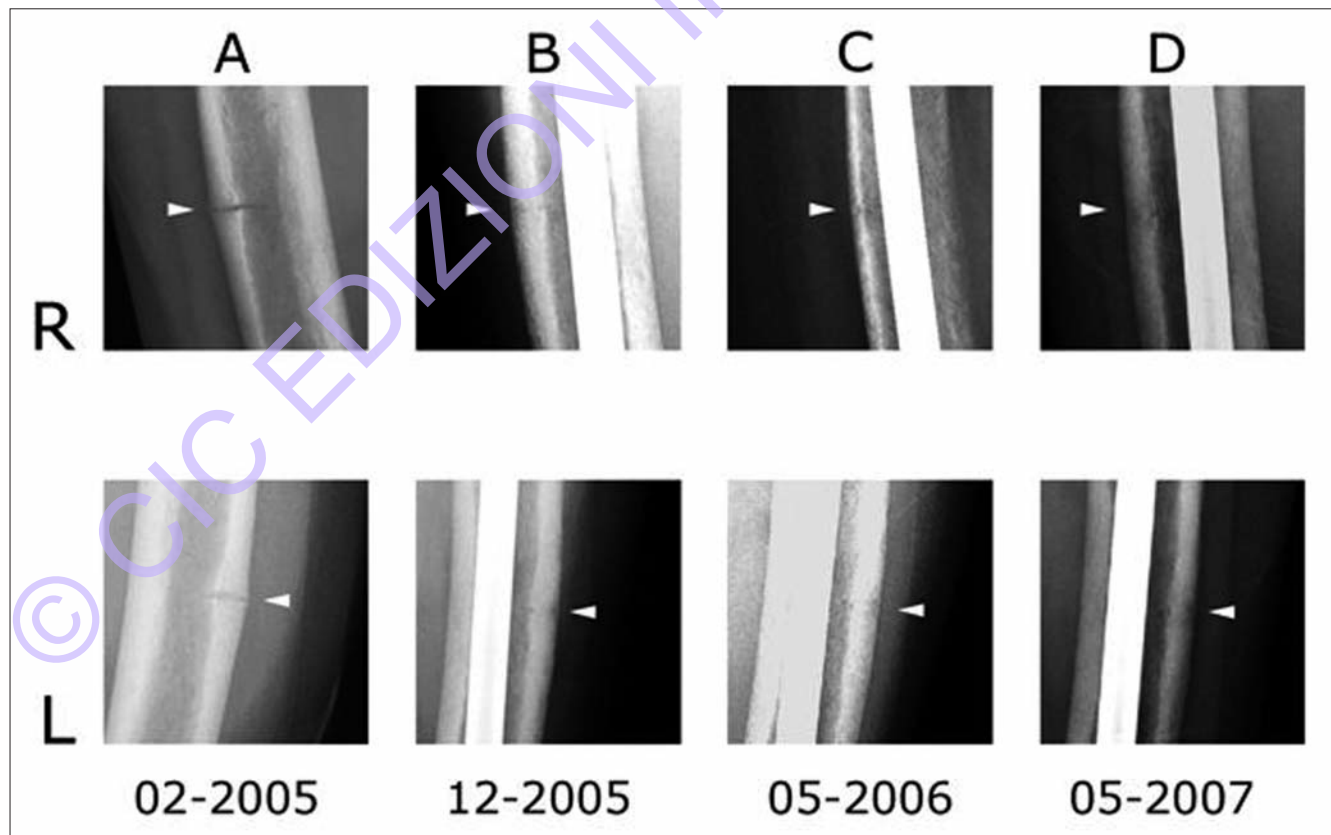


Figure 1 - Bilateral stress fractures in the lateral femur cortices in an adult patient with hypophosphatasia after 2.5 years of risedronate therapy (A). Note that the fractures have not healed 10 months after intra-medullary rod placement (B). Teriparatide was started in Jan 2006. Note progressive healing (C) and resolution of fractures (D) 4 months and 16 months after teriparatide treatment respectively.

Table I - Biochemical response of adult hypophosphatasia patient treated with teriparatide.

	Baseline	2 m	4 m*	7 m	13 m	19 m	22 m	28 m	34 m	Mean on Treatment
	ON TREATMENT WITH TERIPARATIDE									
Serum calcium (8.5-10.5) mg/dL	9.8	10	11	9.2	9.8	-	9.5	9.5	9.6	9.6
Serum phosphorus (2.5-4.5) mg/dL	5.2	5	4.7	4.9	5.2	-	-	-	-	5
Serum alkaline phosphatase (40-150) U/L	20	31	26	21	-	-	-	-	-	26
BSALP (14-43) U/L	-	-	16	13	18	-	54	13	13	22
Intact PTH (10-60) pg/mL	29	24	9	15	16	27	-	-	-	21
25 hydroxy vitamin D (31-80) ng/mL	28	16	-	24	-	31	30	28	-	26
1,25 dihydroxy vitamin D (25-66) pg/mL	30	36	140	45	69	58	34	45	69	51
Serum PLP (18-175) nmol/L	3400	3900	3220	3310	-	-	-	-	-	3605
Urine cross-link-N-telopeptide (14-75) nM/mM creatinine	64	36	151	59	144	44	39	78	95	71

PLP = pyridoxal 5' phosphate.

No changes occurred in the methods of testing for all biochemical variables.

* TPD injections were held the morning of the labs, except the day when the 4 month values were taken. Hence this set is excluded from calculation of mean on treatment.

Creatinine ranged from 0.6 to 0.7 mg/dL (range: 0.07-1.4 mg/dL).

gree of symptomatic improvement was also noted by others (2, 3). However, none of the reported patients were exposed to previous bisphosphonate therapy. It is known that previous antiresorptive therapy may blunt the BMD response to teriparatide (4). However, there may be differences in anabolic responsiveness to teriparatide as a function of the type of prior bisphosphonate exposure (5). Patients exposed to prior risedronate therapy seem to have greater responsiveness to teriparatide than alendronate (5). Prior use of risedronate certainly did not hamper the clinical and radiological response in our patient.

Our patient had interesting biochemical changes during teriparatide treatment. Firstly, levels of 1, 25 (OH)₂ D significantly increased and PTH levels decreased. While the observation that teriparatide increases 1, 25 (OH)₂ D is a known one (6), the question is why should this have developed in the face of decreasing serum PTH levels. Dr. Licata has made a similar observation in other patients treated with teriparatide (7, 8). In his observed cohort, teriparatide treatment caused increase in 1, 25 (OH)₂ D levels in the face of decreasing serum PTH and 25 (OH) D levels. He hypothesizes that teriparatide may be disrupting the normal regulation of vitamin D metabolism.

Secondly, the larger magnitude of rise in urine NTX without antecedent rise in BSALP – without clinical evidence of reduced skeletal fragility – was intriguing. Whyte et. al. made a similar observation in their patient prompting temporary withdrawal of this medication (2). Camacho et. al. also observed that BSALP increased to the low normal range only, coupled with a substantial increase in urine NTX (3).

Our patient's fractures failed to heal 10 months after intramedullary rods were placed. Radiographs taken during teriparatide treatment demonstrated total healing of both femur fractures. Most importantly no new fractures developed in spite

of several falls. Coe et al. have shown more than 20 years ago that pseudofractures in hypophosphatasia respond to intramedullary rodding (9). However, this data is retrospective, and has not been reproduced since. Although, it is conceivable that some of the healing may have occurred due to the orthopedic procedure, in this case, it is our clear impression that teriparatide treatment has contributed to fracture healing. An animal study (10) clearly showed that teriparatide treatment increased BMD and strength, and enhanced fracture healing by producing a sustained anabolic effect throughout the remodeling phase of fracture-healing.

Conclusion

Hypophosphatasia remains a disease for which there is no effective medical therapy. Interestingly, a recent study (11) demonstrated effective prevention of infantile hypophosphatasia in TNALP null mice using a bone-targeted, recombinant form of human TNSALP. In recent months, we and others (2, 3) report use of teriparatide in humans with adult hypophosphatasia with various degrees of clinical success. Our case report supports the use of teriparatide therapy after prior exposure to risedronate and suggests that this drug did not blunt the effect of teriparatide. In conclusion, off-label use of teriparatide may help patients with adult hypophosphatasia.

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