Enhanced Callus Formation After Six Weeks of Parathyroid Hormone Treatment in a Man with Multiple Pelvic Fractures and Osteogenesis Imperfecta Type IV

A Case Report

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Osteogenesis imperfecta (OI) is a genetic disorder involving a defect in collagen synthesis. OI is characterized by impaired bone formation, low bone mass, and deterioration of bone architecture in adults. Typical bone features are a decrease in trabecular thickness and number of trabeculae, as well as thin cortices. As a result, there is increased bone fragility with recurrent fractures, leading frequently to skeletal deformities.

Currently, no supportive therapy for fracture-healing is available, although preclinical studies show promise for the use of teriparatide (parathyroid hormone [PTH] 1-34). We present the case of a patient with multiple pelvic fractures and osteogenesis imperfecta type IV who demonstrated enhanced callus formation after treatment with PTH. The patient was informed that data concerning the case would be submitted for publication and he provided consent.

Case Report

A seventy-eight-year-old man with osteogenesis imperfecta (Sillence type IV) was admitted to the hospital with severe pelvic pain following pelvic fractures in five locations (the superior and inferior pubic rami on both the left and right sides and the sacrum), which had been sustained three months earlier after a fall. The initial office visit had been in a specialized trauma center. The patient had been treated with bisphosphonate therapy (alendronate followed by ibandronate) for a minimum of ten years.

Since the occurrence of the pelvic fractures, the patient had been confined to a wheelchair and had been dependent on analgesics (tramadol hydrochloride, metamizol, diclofenac) for severe, chronic pain. The earlier fracture history had consisted of numerous nonvertebral fractures after minor trauma in the left radius, right malleolus, right thumb, left femoral neck (followed with total endoprosthesis), ilium, and multiple ribs. The spine had been stabilized from T12 to L2, with posterior lumbar interbody fusion for treatment of a vertebral fracture at L1. The medical history also revealed arterial hypertension and a cerebrovascular insult in the basal ganglia that had occurred fifteen years earlier, with a remaining mild left gluteal hemiparesis.

When admitted to the hospital, the patient (body mass index, 30.3; weight, 94 kg; height, 176 cm) was hypertensive. The neurological status revealed reduced strength of the left lower extremity (a result of the prior stroke) and insufficiency of the hip muscles.

Radiographs and multislice computed tomography of the pelvis showed displaced fractures of the pubic and ischial rami on both the right and left sides and a fracture of the sacrum, with minimal callus formation at the fracture sites (Figs. 1-a and 1-b). A spine radiograph revealed multiple fractures of the lumbar and thoracic vertebrae as well as the ribs.

Bone mineral density measurements (measured by dual-energy x-ray absorptiometry) demonstrated moderately decreased T-scores at the radius (−1.9), total hip (−2.4), femoral neck (−3.3), and calcaneus (−3.9), with a decrease of approximately 5% compared with values measured four years earlier. The values at the lumbar spine could not be evaluated because of the prior spinal surgery.

Structure analysis with high-resolution peripheral quantitative computed tomography (SCANCO) showed profound inhomogeneity of the trabecular network and a substantially...
reduced cortical thickness of the radius (0.43 mm) and the tibia (0.25 mm). The indices of trabecular number, thickness, and separation were within the normal range.

Laboratory investigations demonstrated an elevated alkaline phosphatase level (335 U/L; reference range, 40 to 129 U/L). Levels of calcium, phosphate, PTH, and 25-hydroxy vitamin D were all within the normal range. Levels of type-1 collagen cross-linked C-telopeptide and procollagen aminoterminal propeptide type I were suppressed, which was related to the long-term bisphosphonate use. Secondary metabolic bone disorders were excluded with full clinical investigations and blood analysis.

Because of its anabolic effects on bone and the evidence of enhanced fracture-healing in preclinical studies, treatment with teriparatide (20 mg once daily) was initiated to potentially stimulate fracture repair. Additionally, calcium (1000 mg daily) and vitamin D (800 IU daily) were given to prevent vitamin D deficiency and to preserve 25-hydroxy vitamin D levels above the threshold of 30 ng/mL.

After six weeks of treatment with teriparatide, marked increase of callus formation at every fracture site was demonstrated by computed tomography (Figs. 1-c and 1-d).

In addition, pelvic pain decreased substantially, and the patient used fewer analgesic medications. He regained mobility, no longer needed a wheelchair, and could stand and walk without a walker. Serum levels of calcium, phosphate, vitamin D, and PTH remained in the normal range during and after treatment. Type-1 collagen cross-linked C-telopeptide and procollagen aminoterminal propeptide type I were increased, which was a sign of response to teriparatide therapy.

**Discussion**

It is well known that bisphosphonates increase bone mineral density and may reduce fracture risk in children, adolescents, and adults with OI. Therefore, bisphosphonates are the first-choice drugs for routine treatment in these patients. Long-term and/or high-dose pamidronate, however, can result in defective bone remodeling and delayed healing after osteotomy.

PTH and teriparatide may provide some potential clinical benefit in fracture-healing. Although, to our knowledge, the only systemic study with teriparatide did not report convincing results for enhanced fracture-healing, numerous case reports have been published with positive results in bilateral subtrochanteric stress fractures after long-term alendronate treatment, in fractures in adult patients with hypophosphatasia, in fractures of the distal part of the radius, in sternal fractures, and in humeral fractures.

Numerous preclinical studies have been published on the effects and mechanism of action of PTH on fracture-healing. Andreassen et al. showed that intermittent PTH treatment (60 μg/kg daily in one group and 200 μg/kg daily in another group) increased the ultimate load and the external callus volume of fractures after forty and twenty days, respectively, in rats. Nakajima et al. treated rats with PTH (1-34) (10 mg/kg daily) after fracture and found increased bone mineral density, bone mineral content, and ultimate load of the callus after twenty-eight and forty-two days of treatment. In addition, callus formation was enhanced by an early stimulation of proliferation and differentiation of osteoprogenitor cells. In a study of rats with femoral fracture, Alkhiary et al. found that those treated with 30 μg/kg of PTH (1-34) daily showed an increased stiffness, bone mineral content, bone mineral density, cartilage volume, and torsional strength after twenty-one days of treatment compared with controls. Interestingly, after day thirty-five, even the low-dose group (treated with only 5 μg/kg of PTH [1-34] daily) showed substantial increases in bone mineral content, bone mineral density, and total osseous...

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**Fig. 1**

**Figs. 1-a through 1-d** Monitoring of fracture-healing by pelvic multislice computed tomography. **Fig. 1-a** Axial image at baseline three months after the fractures. **Fig. 1-b** Enlarged view of the bilateral sacral fractures at baseline. **Fig. 1-c** Axial image after six weeks of treatment with teriparatide. **Fig. 1-d** Enlarged view showing healing progress with narrowing of the fracture gap, new bone, and callus formation.
tissue volume. Intermittent PTH (1-34) therapy results in higher bone strength, bone mineral content, and mineralized tissue volume during distraction osteogenesis.

PTH (1-34) influences the callus formation in the early proliferation and differentiation of osteoprogenitor cells two and four days after fracture. PTH (1-34) is also associated with an enhanced formation rate of chondroprogenitor cells, chondrocyte maturation, and chondrocyte mineralization, which are all important for endochondral ossification. A recent study showed that PTH (1-84) accelerates fracture-healing in pelvic fractures and improves functional outcome in patients with osteoporosis. To the best of our knowledge, our case report is the first to describe a patient with OI and recent fractures who demonstrated typical radiographic signs of callus formation after receiving treatment with teriparatide. These signs of accelerated fracture-healing were associated with clinically marked improvement of mobility: the patient regained mobility after the sixth week of osteoinductive treatment and no longer needed a wheelchair. This case suggests that additional research is necessary to evaluate the potential benefit of teriparatide in the treatment of adult patients with OI.

References