# Systemic Teriparatide Administration Promotes Osseous Regeneration of an Intrabony Defect: A Case Report

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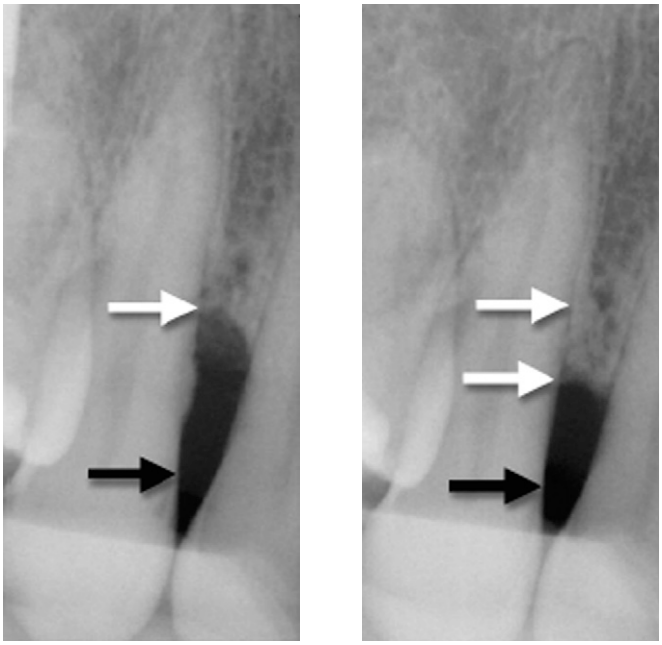

**Introduction:** Teriparatide comprises the first 34 amino acids of parathyroid hormone and is a systemic anabolic agent that is Food and Drug Administration approved for the treatment of osteoporosis but not for periodontitis. To our knowledge, this is the first clinical case report to document the treatment of a patient with severe periodontitis using an open-flap debridement procedure in conjunction with teriparatide.

**Case Presentation:** A 45-year-old female patient was diagnosed with severe chronic periodontitis, including the presence of an intrabony defect on tooth #6. She received open-flap debridement surgery in conjunction with daily systemic administration of 20 μg teriparatide, oral vitamin D, and calcium supplements for 6 weeks. Radiographic, clinical, gingival crevicular fluid (pyridinoline cross-linked carboxy-terminal propeptide of type I procollagen, procollagen type 1 N-propeptide, and osteocalcin), and serum parameters (parathyroid hormone, bone alkaline phosphatase, calcium, and 25-hydroxyvitamin D) were assessed. Treatment outcomes were evaluated over 4 years, with successful radiographic and clinical results throughout the follow-up period.

**Conclusion:** Teriparatide administration in conjunction with traditional open-flap debridement surgery offers potential for the treatment of severe intrabony defects resulting from chronic periodontitis. *Clin Adv Periodontics* 2012;2:66-71.

**Key Words**: Bone regeneration; guided tissue regeneration; parathyroid hormone; periodontal attachment loss; periodontal bone loss; teriparatide.

## Background

Traditional periodontal surgical procedures, such as open-flap debridement, most often result in tissue repair without true regeneration of the lost tissues.[1] Approaches to treat periodontitis aimed at periodontal regeneration include techniques, such as guided tissue regeneration (GTR) and the use of local and systemic biologic modifiers, such as platelet-derived growth factor, fibroblast growth factor, low-dose doxycycline, and enamel matrix derivative (EMD). Although these regenerative approaches have shown success,

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none is capable of regenerating all types of periodontal defects in every situation. Consequently, there is still a critical need for a therapy that can enhance periodontal regeneration in a predictable manner.

Parathyroid hormone (PTH) is an endogenous hormone with both catabolic and anabolic properties in bone, depending on the concentration and dosing regimen. Teriparatide contains the first 34 amino acids of the PTH molecule and is the only commercially available pharmacologic agent in the United States for treating osteoporosis that has been shown in multicenter clinical trials to increase bone mass lost as a result of osteoporosis.[2] However, teriparatide is not approved by the US Food and Drug Administration for the treatment of periodontitis. Because osteoporosis and periodontitis share aspects of their pathophysiology,[3] there is justification for considering the treatment of periodontal disease with therapies used for osteoporosis. This led to the first human clinical trial using teriparatide to enhance healing in the oral cavity in 40 patients with advanced periodontal disease.[4] The results of the clinical trial demonstrated that patients taking teriparatide experienced significantly greater radiographic linear bone gain, probing depth (PD) reduction, and clinical attachment level (CAL) gain compared to patients taking placebo. This case report documents the treatment and long-term follow-up of a patient from this human clinical research trial who was treated with teriparatide in conjunction with periodontal surgery (ClinicalTrials.gov no. NCT00277706).

## Clinical Presentation

A 45-year-old white female presented to the Michigan Center for Oral Health Research (Ann Arbor, Michigan) on November 17, 2005, as part of a clinical research trial for the treatment of an intrabony defect on the mesial aspect of tooth #6 (#6M) associated with generalized severe chronic periodontitis.[4] The University of Michigan Institutional Review Board approved the study. The patient was generally healthy except that she had been recently diagnosed with osteopenia and was a former smoker (12 packs/year history; quit in 1990). She reported no known drug allergies and no current medications. Scaling and root planing of all teeth was performed in October 2005 at the University of Michigan School of Dentistry. After initial therapy, PDs at tooth #6M were 7 mm on both the mesio-buccal and mesio-palatal surfaces (Table 1). CAL was 9 mm on the mesio-buccal surface and 7 mm on the mesio-palatal surface. Bleeding on probing (BOP) was present in the area as well.

## Case Management

On January 18, 2006, the patient received traditional open-flap debridement surgery in the maxillary right quadrant (surgeon was RME) (Fig. 1). During surgery, the intrabony component of the defect measured 2 mm on the buccal surface and 3 mm on the lingual surface. Three days before surgery, the patient began taking 20 µg teriparatide, 1,000 mg calcium, and 800 IU vitamin D daily and continued this regimen for 6 weeks.

## Clinical Outcomes

Clinically, surgery resulted in satisfactory outcomes, with periodontal PDs returning to healthy levels within 9 months. At 9 months, PDs were 2 mm on both the palatal and buccal aspects of tooth #6M. CAL measured 6 mm on the mesio-buccal surface and 4 mm on the mesio-palatal surface. At both the 1 and 4 year follow-up appointments, PDs were 3 mm and CAL was 7 mm on the mesio-buccal surface and 6 mm on the mesio-palatal surface, indicating long-term stability.

Standardized periapical radiographs were taken before surgery, every 3 months afterward for 1 year, and again at a 4-year follow-up (Figs. 2a through 2c). The initial defect depth, as assessed radiographically, measured 6.1 mm from the cemento-enamel junction (CEJ) to the base of the defect. Maximum defect resolution was attained at 9 months post-surgically, with 2.3 mm reduction in radiographic defect depth, corresponding to near-complete osseous fill of the intrabony defect based on intraoperative measurements. Digital subtraction radiography was also used to confirm

**TABLE 1** Clinical and Radiographic Results for Tooth #6M

| Clinical and Radiographic Measurements | Baseline | | 1 Year | | 4 Year | |
|---|---|---|---|---|---|---|
| | Mesio-Buccal | Mesio-Palatal | Mesio-Buccal | Mesio-Palatal | Mesio-Buccal | Mesio-Palatal |
| Clinical measurements | | | | | | |
| CAL (mm) | 9 | 7 | 7 | 6 | 7 | 6 |
| PD (mm) | 7 | 7 | 3 | 3 | 3 | 3 |
| BOP | Yes | Yes | Yes | No | No | No |
| Radiographic measurements | | | | | | |
| Intrabony defect depth (mm) | 2.3 | | 0 | | 0 | |
| Alveolar bone height (CEJ to base of defect,[mm]) | 6.1 | | 3.8 | | 4.0 | |

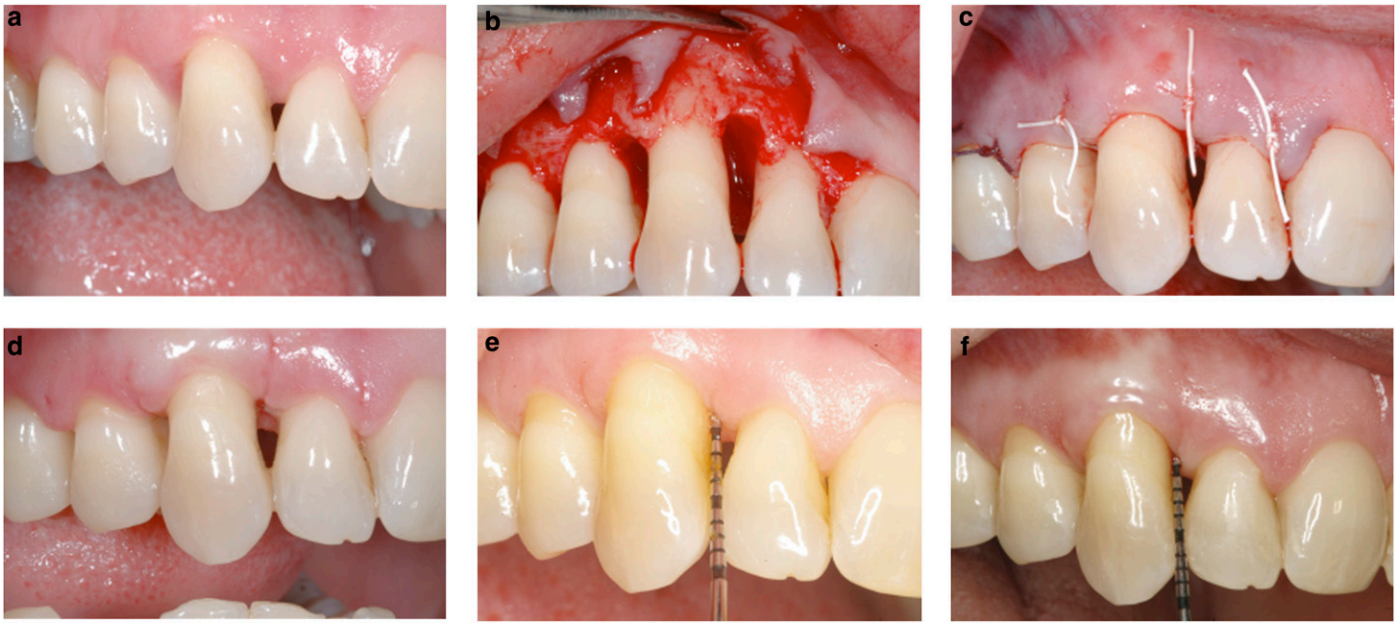


**FIGURE 1a** Preoperative image of tooth #6. **1b** Open-flap debridement with an intrabony defect noted on tooth #6M. **1c** Sutured flap using simple, interrupted sutures. **1d** One week postoperative healing is within normal limits. **1e** After 12 months of healing, PDs were reduced to 3 mm. **1f** Four years after surgery, PDs on tooth #6M remain stable with no BOP.

near-complete intrabony defect fill at 9 months (Fig. 2d). This result was stable over a 4-year period, although the crestal lamina dura appeared less dense than at 9 months post-surgically. Cone beam computed tomography (CBCT) scans taken before surgery and at 12 months also confirmed positive changes in the defect morphology, including modest vertical bone gain on tooth #6M (Figs. 2e and 2f).

As part of the research trial, serum calcium, 25-dihydroxy-vitamin D, PTH, and bone alkaline phosphatase were measured (Table 2). At the time of surgery, all serum parameters were within normal limits. The effect of vitamin D and calcium supplementation is discussed in detail in a separate publication.[5] Six weeks after surgery, which corresponded to the end of the teriparatide dosing regimen, the patient's serum bone alkaline phosphatase levels were slightly elevated, a reflection of compliance with teriparatide administration. Gingival crevicular fluid (GCF) samples of bone turnover markers, including pyridinoline cross-linked carboxy-terminal propeptide of type I procollagen (ICTP), osteocalcin (OCN), and procollagen type 1 N-propeptide (P1NP), were evaluated at baseline, 6 weeks, 6 months, and 1 year and analyzed by standard methodologies.[6] In addition, a dual energy x-ray absorptiometry (DXA) scan was performed to evaluate systemic bone mineral density before surgery and at 1 year. P1NP, a marker of bone formation, was elevated at 6 weeks after surgery. ICTP and OCN, markers of bone resorption and bone turnover, respectively, decreased over time. The patient had *T* scores of −1.2 (femur) and −0.9 (spine) before surgery; at 1 year, the *T* scores were −0.3 (femur) and −0.8 (spine).

## Discussion

This case report demonstrates that teriparatide administration in conjunction with periodontal surgery resulted in improved clinical and radiographic outcomes that were sustained for 4 years. The patient in this report had greater improvement in clinical and radiographic parameters than the average improvement reported in previous studies.[7,8] This was a proof-of-principal study using an open-flap debridement protocol and so the improvements noted as a result of teriparatide administration would ideally be optimized in future studies, perhaps as an adjunct to GTR procedures. Future studies are also necessary to determine the inclusion criteria, indications, and optimum dosing regimen for this treatment approach.

The effect of systemic teriparatide administration on the periodontium in humans had not been documented before this clinical trial,[4] so little is known about its therapeutic potential for the treatment of oral conditions. One study evaluated the ability of teriparatide to aid in fracture repair and found that it preferentially enhanced bone remodeling in areas of high turnover, such as fracture and surgical sites.[9] In an animal study of mandibular fracture healing, systemic teriparatide administration enhanced early-phase wound healing.[10] Another recent study assessed the osteogenic effect of teriparatide on various parts of the human skeleton and found that the mandible had one of the highest activity rates.[11] This may explain why systemic teriparatide administration resulted in such high clinical success when used as an adjunct to an oral surgical procedure. Additionally, this suggests that the oral cavity may be one of the most receptive sites in the body for teriparatide response.

Side effects of systemic teriparatide administration include dizziness, nausea, swelling at the injection site, and joint pain. In preclinical studies,[12] there was an increased incidence of osteosarcoma in teriparatide-treated rats at doses much higher and much longer duration than used for this application. The relevance of these findings is uncertain because an increased incidence of osteosarcoma has not been found in humans treated with teriparatide, but it is currently

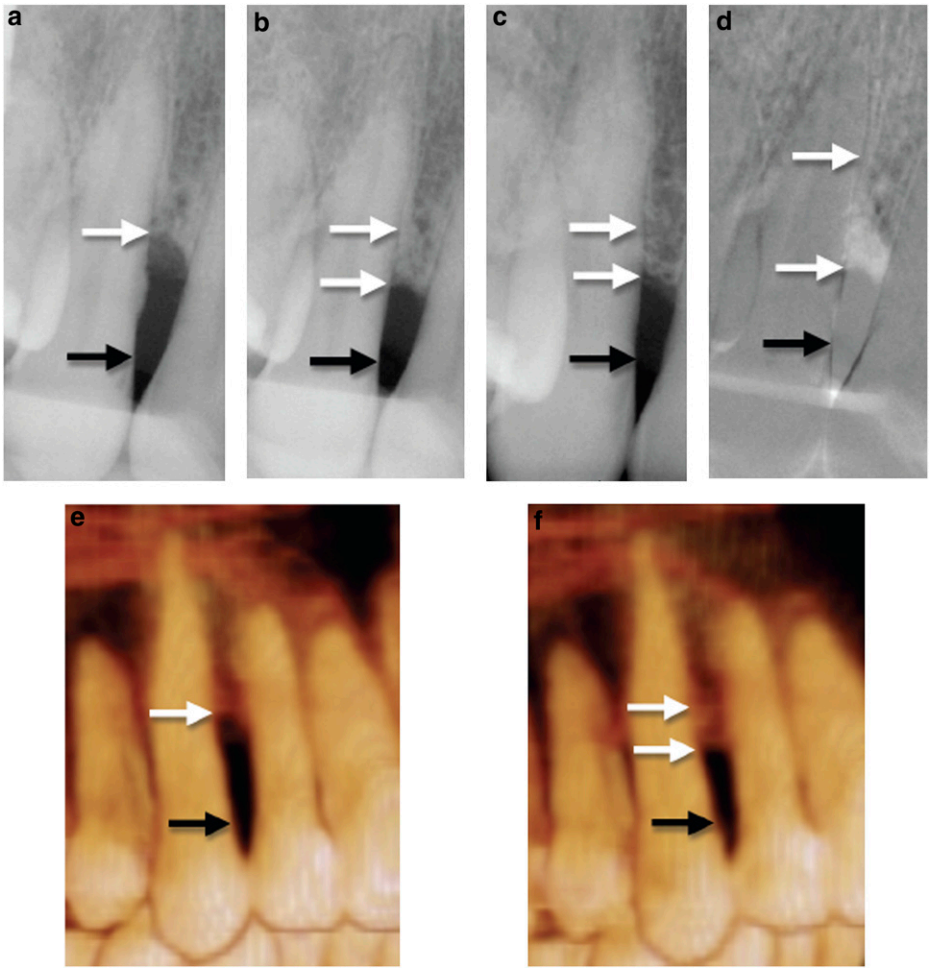


**FIGURE 2** Imaging of the defect presented in Figure 1. **2a** Initial radiograph illustrating an intrabony defect on tooth #6M. **2b** Radiograph at 9 months demonstrating significant defect fill. **2c** Four years after surgery, significant bone fill remains. **2d** Digital subtraction radiography shows the area and degree of bone fill on tooth #6M from baseline to 9 months. **2e** Reconstructed CBCT image of the maxillary right quadrant before surgery. **2f** Reconstructed CBCT image of the maxillary right quadrant 1 year postoperatively. In all panels, white arrows represent the baseline bone level as well as the current bone level. Black arrows illustrate the reference point from which measurements were obtained.

contraindicated for patients at increased baseline risk of osteosarcoma. In addition, the cost of teriparatide administration in its current form is very high relative to other treatment regimens. Periodontitis is a localized disease compared to osteoporosis, and so future strategies to optimize teriparatide administration could include local concentration in sites of osseous wound healing to maximize benefits and minimize systemic effects. However, it is challenging to develop a local delivery system that is able to deliver teriparatide at low and intermittent doses, which is what is required to achieve anabolic effects. Several local delivery systems have been developed already and tested in preclinical animal models with varying rates of success.[13,14] In foxhounds, an arginine–glycine–aspartic acid modified polyethylene glycol-based matrix containing covalently bound peptides of PTH resulted in significantly more new bone formation but not more bone-to-implant contact after 4 and 12 weeks.[13] In contrast, systemic PTH administration in a rat model was found to stimulate local bone formation, whereas local delivery of PTH using β-tricalcium phosphate did not.[14]

There is a clear need for improved therapeutics that can target localized osseous healing as desired for periodontal regenerative outcomes. Using systemic teriparatide as an adjunct to periodontal surgery may be a promising therapeutic option to promote osseous regeneration with long-term results. However, it is important to note that the ability of teriparatide to promote regeneration has not been verified histologically. Furthermore, future large-scale clinical trials are required to confirm the benefits of teriparatide on osseous healing and to optimize treatment protocols. ■

**TABLE 2** Serum, GCF, and DXA Results

| Serum, GCF and Radiographic Assessments | Baseline | 6 Weeks | 6 Months | 12 Months |
|---|---|---|---|---|
| Serum biomarkers | | | | |
| PTH (pg/mL) | 36 | N/A | N/A | N/A |
| Calcium (mg/dL) | 9.7 | 9.7 | 9.1 | N/A |
| 25-dihydroxyvitamin D (ng/mL) | 33 | 24 | 34 | N/A |
| Bone alkaline phosphatase (μg/L) | 7.4 | 8.7 | 7.8 | N/A |
| GCF | | | | |
| ICTP (pg/μL) | 90 | 67 | 46 | 21 |
| OCN (pg/μL) | 35 | 29 | 18 | 12 |
| P1NP (pg/μL) | 1,151 | 1,296 | 394 | 97 |
| Systemic bone mineral density (assessed using DXA) | | | | |
| *T* score, spine | −0.9 | N/A | N/A | −0.8 |
| *T* score, femur | −1.2 | N/A | N/A | −0.3 |

## Summary

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|---|---|
| **Why is this case report new information?** | ■ To our knowledge, this is the first fully documented case of systemically administered teriparatide to aid in the surgical treatment of periodontitis. |
| **What are the keys to successful management of this case?** | ■ A 6-week dosing regimen of teriparatide resulted in long-lasting clinical improvement, suggesting that this is a promising therapeutic option for patients with severe periodontitis. |
| **What are the primary limitations to success in this case?** | ■ Open-flap debridement surgery was used as part of this proof-of-principle study. In the future, other surgical options could be explored that may yield better outcomes. |

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○ indicates key references.