

CASE REPORT

OPEN ACCESS

Full open access to this and thousands of other papers at <http://www.la-press.com>.

Role of Teriparatide in Accelerating Metatarsal Stress Fracture Healing: A Case Series and Review of Literature

Pooja Raghavan¹ and Elena Christofides²

¹Department of Medicine, ²Department of Medicine, Division of Endocrinology, Mount Carmel Health, Columbus, OH.
Corresponding author email: christofides@endocrinology-associates.com

Abstract: Bone fractures are one of the leading causes of emergency room visits worldwide, with approximately 8 million bony fractures occurring annually in the US alone. Although the majority of fractures do not cause significant long-term morbidity and mortality, approximately 10% of these fractures result in impaired fracture healing, drastically affecting quality of life in affected patients. By increasing bone formation, teriparatide, an anabolic agent used in the treatment of postmenopausal osteoporosis, has shown promise in accelerating the rate of fracture healing. We present two patients with impaired healing of metatarsal fractures who were subsequently treated with teriparatide. Both patients experienced successful bony union of the fracture after the use of teriparatide. These findings suggest that teriparatide may be useful in the clinical setting for the acceleration of fracture healing, especially in patients who are at risk for impaired fracture healing.

Keywords: teriparatide, bone, fracture healing

Clinical Medicine Insights: Endocrinology and Diabetes 2012:5 39–45

doi: [10.4137/CMED.S9663](https://doi.org/10.4137/CMED.S9663)

This article is available from <http://www.la-press.com>.

© the author(s), publisher and licensee Libertas Academica Ltd.

This is an open access article. Unrestricted non-commercial use is permitted provided the original work is properly cited.



Introduction

Bony fractures are one of the most common reasons for physician visits worldwide. With greater public interest in physical fitness activities to maintain a healthy lifestyle, metatarsal stress fractures are commonly encountered by clinicians. Metatarsal stress fractures, which account for nearly 25% of all stress fractures, often heal with nonoperative measures. Immobilization of the foot and avoidance of strenuous activity often result in bone healing and return to full functional capacity within 6–8 weeks of the initial injury.

Impaired fracture healing in which a patient may fail to form a unionization of bone, or have delayed unionization, is frequently encountered in both inpatient and outpatient settings. Patients at risk for impaired fracture healing include elderly patients, diabetics, smokers, patients with osteoporosis, and postmenopausal females due to estrogen deficiency. Impaired fracture healing can have devastating consequences in this patient population, and may increase the fracture-related morbidity and mortality.

Teriparatide, a drug approved for the treatment of osteoporosis in postmenopausal women, has shown promise in the realm of fracture healing. In the initial stages of fracture healing, an increase in bone formation is required. By increasing bone formation through stimulation of osteoblasts, teriparatide may accelerate the natural healing process of fractures. This may be useful in treatment of patients who have impaired fracture healing, ultimately affecting quality of life.

We present two cases of women with metatarsal fractures who had risk factors for impaired fracture healing, and report the time to fracture healing with the use of teriparatide.

Case Presentation

Case 1

A 35-year-old premenopausal Caucasian female presented to the emergency department with a complaint of pain in her right foot which occurred abruptly while running. She described the pain as sharp and unremitting, and denied any recent trauma to the affected foot. Medical history was significant for a stress fracture of the left second metatarsal two years prior, which took approximately 14 weeks to obtain radiographic evidence of fracture healing with the use

of an immobilizing boot. She denied the use of any medications, alcohol, or illicit drugs, but did have a 21 pack-year history of tobacco use.

Physical examination revealed a well developed female in mild distress. On examination of the right foot, there was the presence of nonpitting edema on the dorsal foot. Range of motion testing in the right ankle revealed decreased dorsiflexion. Radiography of the right foot was consistent with a stress fracture at the base of the fifth metatarsal with associated soft tissue inflammation (Fig. 1). The patient was instructed to wear an immobilizing boot on the right foot and to avoid strenuous activity. Ibuprofen was suggested to the patient for analgesia.

Nearly 6 weeks after sustaining the fracture, the patient returned to the emergency department with continued pain in the right foot despite the use of



Figure 1. Radiography of right foot consistent with a stress fracture of the fifth metatarsal (arrow).

the immobilizing boot and adequate analgesia. Radiography was repeated, which revealed no change compared with initial imaging. The patient refused further use of the immobilization boot. Due to non-compliance with the immobilization boot, she was started on a daily dose of teriparatide, 50,000 IU of vitamin D3, and 2000 mg of calcium citrate.

Four weeks into therapy with teriparatide, repeat imaging revealed evidence of bony callus and new bone formation of the right fifth metatarsal, consistent with a healing fracture (Fig. 2). The patient was

pain free at this time, and shortly thereafter resumed all prior activities, including running.

Case 2

A 40-year-old Caucasian female was seen in the orthopedic clinic with complaints of moderate pain in her left foot. She described the pain as sharp, and worsening with movement of her left foot. Medical history was significant for hypothyroidism secondary to Hashimoto's disease, celiac disease, and premature ovarian failure. She had no history of osteoporosis but had a previous fracture of the right distal radius, which took approximately 10 weeks to heal as per clinical findings and imaging studies. Home medications included vitamin D3 50,000 IU weekly, levothyroxine 175 μ g daily, and glucosamine/chondroitin sulfate 1500 mg/1200 mg daily. She denied the use of tobacco, alcohol, or illicit drugs.

Physical examination was significant for tenderness to palpation of the left foot, with the point of maximal tenderness being over the first phalanx. Radiography of the left foot confirmed the presence of a first left phalanx stress fracture (Fig. 3), and the patient was instructed to wear an immobilizing boot for at least 6 weeks. Because the patient appeared to be reluctant to wear an immobilizing boot for such a long duration, she was also started on teriparatide, 50,000 IU of vitamin D3 daily, and calcium citrate 2000 mg daily. She continued this medication regimen without any additions or changes for a total duration of 4 weeks.

One week into therapy with teriparatide, the patient's pain and swelling had subsided and she was able to remove her immobilizing boot. At the end of 4 weeks, repeat imaging revealed a fracture that was well healed with callus formation seen (Fig. 4). The patient had resumed full activities, and teriparatide was discontinued at this time.

Discussion

Bony fractures are the most frequent cause of emergency room visits worldwide. The incidence of fractures has been steadily increasing, with an estimated 15.3 million fractures occurring in the US annually.^{1,2} Stress fractures of the metatarsal bones are common, and account for approximately 5% of fractures seen in the primary care setting annually.³ With the treatment of metatarsal stress fractures based primarily



Figure 2. Radiography of right foot revealing a well healing fifth metatarsal fracture with callus formation (arrow), 4 weeks after initiation of teriparatide.



Figure 3. Radiography of left foot consistent with a fracture of the first metatarsal (arrow).

on conservative measures such as immobilization, the morbidity associated with such fractures depends largely on the rate of an individual's natural fracture healing time.

The pathophysiology of fracture healing is complex, occurring in four phases. The first phase involves inflammation and formation of a hematoma at the site of fracture due to disruption of the blood supply at the site of injury.⁴ In the second phase, chondrogenesis begins and a soft callus forms, which is then mineralized.⁴ The third phase marks the beginning of osteoblast cells forming woven bone, resulting in formation of a hard callus and union of the fracture.⁵ In the final phase of fracture healing, remodeling of bone occurs, resulting in the formation of lamellar bone, which is mechanically stronger bone.⁵

Stress fractures of the metatarsal bones are often misdiagnosed initially as a soft tissue injury,



Figure 4. Radiography of left foot revealing a well healed fracture of first metatarsal with callus formation (arrow), 4 weeks after initiation of teriparatide.

because initial radiographs may not show evidence of fracture.⁶ If clinical suspicion for a metatarsal stress fracture is high, or diagnosis is confirmed via radiographic imaging, conservative treatment modalities are first-line options. Patients with metatarsal stress fractures should refrain from vigorous physical activity, and immobilization of the affected foot is often recommended. In most cases, nonweight-bearing activity and placement of an immobilizing boot leads to decreased pain associated with metatarsal fractures. Under normal circumstances, it takes approximately 6–8 weeks for a metatarsal stress fracture to heal.⁷ A visible callus is typically seen on radiographs by 6 weeks after the initial injury.⁶



However, in approximately 10% of patients, impaired fracture healing is encountered, leading to delayed union or nonunion of metatarsal stress fractures.

Fractures of the fifth metatarsal are slightly different from fractures of the other metatarsals. These fractures take longer to heal because of the poor blood supply in the region of the fifth metatarsal. Patients can suffer an avulsion fracture or a Jones fracture. Avulsion fractures involve the most proximal part of the fifth metatarsal called the tuberosity. They typically show radiographic evidence of union within 8 weeks with immobilization and use of a rigid boot.⁸ Jones fractures involve the proximal diaphysis, and without surgery, take approximately 20 weeks to heal.⁸ Avoiding weight-bearing is usually recommended for several months, and many patients find it difficult to comply with this. Half of these fractures treated with immobilization alone tend to result in refracture or nonunionization of the fracture.⁹ Thus many patients, including athletes, opt for surgical intervention to minimize the healing time. This involves placement of a screw into the canal of the fifth metatarsal, followed by immobilization for at least 2 weeks.¹⁰ With surgery, these fractures typically heal within 6–8 weeks. However, nonunionization can occur, even after surgery.

Although the pathophysiology of impaired fracture healing is largely unknown, certain risk factors have been well reported. Mechanical causes, such as insufficient immobilization of the fracture, distraction of fracture fragments by fixation devices, or repeated manipulations of a fracture, may lead to delayed or impaired union. Nonmechanical risk factors, including patient comorbidities, have also been suggested to result in impaired fracture healing. Diabetes, smoking, osteoporosis, and estrogen deficiency have all been identified as possible risk factors for impaired fracture healing.¹¹ In such patient populations, impaired fracture healing may result in significant morbidity and negatively impact quality of life.¹² With established risk factors for impaired fracture healing identified, there comes a greater need for therapy that can accelerate fracture healing in patients at high risk for delayed union or nonunion fractures.

Teriparatide, a recombinant human parathyroid hormone analog (1–34), was approved in 2002 by the Food and Drug Administration for the treatment of osteoporosis in postmenopausal women who

are at high risk for fractures.¹³ The only anabolic agent available for the treatment of osteoporosis, its mechanism of action is unique in comparison with other agents used currently. Chronic exposure to endogenous human parathyroid hormone leads to an increase in bone resorption via stimulation of osteoclasts, further exacerbating the condition of osteoporosis.¹⁴ Teriparatide, because of its ability to reach peak serum concentrations in 30 minutes and return to nondetectable serum levels in a few hours, has the paradoxical effect of stimulating new bone formation by favoring stimulation of osteoblasts over osteoclasts.¹⁴ In the natural process of fracture healing, a transient increase in bone formation at the site of fracture occurs. By increasing cortical thickness and bone formation on all bone surfaces, teriparatide may accelerate and augment this process of increased bone formation and fracture healing that happens naturally.⁴

Andreassen et al were the first to report accelerated healing of fractures with teriparatide. Their study involved administering teriparatide to rats with tibial fractures. The results demonstrated enhanced callus formation and mechanical strength of tibial fractures in rats treated with teriparatide.^{15,16} In 2006, Manabe et al used teriparatide for fracture healing in cynomolgus monkeys, because their bone remodeling systems are closest to those of humans.¹⁷ In the study by Manabe et al, the results suggested that by attenuating the degree of mineralization and shrinking the size of the callus, teriparatide may have accelerated the rate of fracture healing.¹⁷ Although prior case studies regarding the use of teriparatide for accelerated fracture healing in humans exist, the only randomized, double-blind study in humans testing the hypothesis of acceleration of fracture repair was done by Aspenberg et al in 2010. In this study, involving 102 postmenopausal women with fractures of the distal radius, it was concluded that there was a shortened time of fracture healing in a group of patients using 20 µg of teriparatide compared with placebo.¹⁸ Their results suggest that teriparatide may lead to acceleration of fracture healing in humans.¹⁸

Our cases reported here suggest the possibility of accelerating metatarsal stress fracture healing with the use of teriparatide. The cost of teriparatide is approximately 600 dollars for a one-month supply.¹³ Taking cost into account, it may be best used to accelerate



fracture healing in those patients at high risk for delayed union or nonunion of fractures, or in patients who require a return to baseline activity at a faster rate than is possible with the normal healing process. This includes high-performance athletes, but also includes a large percentage of the workforce where jobs entail manual labor or constant walking throughout the day. For those who have occupations that involve walking throughout the day, repeated stress on the foot from walking could delay healing of the fracture. Patients with jobs entailing manual labor may suffer a greater loss of income than the cost of teriparatide for one month, due to inability to return to work until healing of the metatarsal fracture has occurred. In addition, many employers may not allow for a month away from work, and this could result in loss of employment for the patient.

According to data from the Centers for Disease Control published in 1990, the value of lost wages stemming from health conditions related to both physical and mental impairment as well as costs of medical care related to this reaches over a billion dollars in the US annually.¹⁹ Therefore, in patients with jobs where the loss of income is greater than the cost of treatment with teriparatide, the drug may be useful in acceleration of fracture healing, allowing earlier return to work.

Although teriparatide is also indicated for the treatment of osteoporosis associated with use of long-term systemic glucocorticoids in men, there have been no data published on the use of teriparatide in the acceleration of fracture healing in men and premenopausal women. There are ongoing Phase II and Phase II clinical trials investigating the benefits of this medication in these specific patient populations. Although more randomized, double-blind, placebo-controlled trials in humans will need to be pursued to investigate further the potential of this drug in fracture healing, clinicians should be aware that teriparatide may become useful in the clinical setting for acceleration of fracture healing.

Author Contributions

Conceived and designed the experiments: PR. Analysed the data: PR. Wrote the first draft of the manuscript: PR. Contributed to the writing of the manuscript: PR, EC. Agree with manuscript results and conclusions: PR, EC.

Jointly developed the structure and arguments for the paper: PR, EC. Made critical revisions and approved final version: EC. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Written consent was obtained from both subjects discussed in this manuscript to use any clinical information and images pertaining to them.

References

1. Burge RT, Dawson-Hughes B, Solomon D, et al. Incidence and economic burden of osteoporotic fractures in the United States, 2005–25. *J Bone Miner Res*. 2007;22:465–75.
2. American Academy of Orthopedic Surgeons. Half of all musculoskeletal injuries occur in the home. Available at: <http://www.aaos.org/news/aaos-now/apr09/clinical9.asp>. Accessed Apr 26, 2012.
3. Hatch R, Alsobrook J, Clugston J. Diagnosis and management of metatarsal fractures. *Am Fam Physician*. 2007;76:817–26.
4. Bukata S, Puzas JE. Orthopedic uses of teriparatide. *Curr Osteoporos Rep*. 2010;8:28–33.
5. Marsh D, Li G. The biology of fracture healing: optimizing outcome. *Br Med Bull*. 1999;55:856–69.
6. Weinfeld S, Haddad S, Myerson M. Metatarsal stress fractures. The Institute for Foot and Ankle Reconstruction at Mercy. *Clin Sports Med*. 1997;16:319–38.
7. The Institute for Foot and Ankle Reconstruction at Mercy. Metatarsal stress fractures. Available at: <http://www.mdmercy.com/footandankle/research%5Fpubs/pressitem57.html>. Accessed Apr 26, 2012.
8. American Academy of Orthopedic Surgeons. Stress fractures of the foot and ankle. Available at: <http://orthoinfo.aaos.org/topic.cfm?topic=a00379>. Accessed Apr 26, 2012.
9. Quill GE Jr. Fractures of the proximal fifth metatarsal. *Orthop Clin North Am*. 1995;26:353.
10. Nunley JA. Fractures of the base of the fifth metatarsal: the Jones fracture. *Orthop Clin North Am*. 2001;32:171.
11. Ellegaard M, Jorgensen NR, Schwarz P. Parathyroid hormone and bone healing. *Calcif Tissue Int*. 2010;87:1–13.



12. Ensrud KE, Thompson DE, Cauley JA, et al. Prevalent vertebral deformities predict mortality and hospitalization in older women with low bone mass. Fracture Intervention Trial Research Group. *J Am Geriatr Soc.* 2000;48:241–9.
13. Forteo® (teriparatide, full prescribing information). Indianapolis, IN: Eli Lilly and Company; 2002.
14. Deal C, Gideon J. Recombinant human PTH 1–34 (Forteo): an anabolic drug for osteoporosis. *Cleve Clin J Med.* 2003;70:585–601.
15. Andreassen TT, Ejersted C, Oxlund H. Intermittent parathyroid hormone (1–34) treatment increases callus formation and mechanical strength of healing rat fractures. *J Bone Miner Res.* 1999;14:960–8.
16. Andreassen TT, Fledelius C, Ejersted C, et al. Increases in callus formation and mechanical strength of healing fractures in old rats treated with parathyroid hormone. *Acta Orthop Scand.* 2001;72:304–7.
17. Manabe T, Mori S, Mashiba T, et al. Human parathyroid hormone (1–34) accelerates natural fracture healing process in the femoral osteotomy model of cynomolgus monkeys. *Bone.* 2007;40:1475–82.
18. Aspenberg P, Genant HK, Johansson T, et al. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. *J Bone Miner Res.* 2010;25:404–14.
19. [No authors listed]. Prevalence of work disability—United States, 1990. *MMWR Morb Mortal Wkly Rep.* 1993;42:757–9.