Case Report Journal of Clinical Orthopaedics 2024 July-December;9(2):118-122

# Bisphosphonate-Induced Atypical Femoral Fractures: Pathogenesis Insights and the Role of Bioactive Collagen Peptides – A Case Report

Somasekhara Reddy Nallamilli[1], Mohan Krishna Althuri[1], Shruti Patwal[2], Manish R Garg[3]

## Abstract

**Introduction:** Bisphosphonates (BPs) have emerged as the mainstay of osteoporosis treatment. However, over the past 10 years, atypical femoral fractures (AFFs) have been identified as a possible side effect of BP.

**Case Report:** A 73-year-old male with a history of prostate carcinoma and an isolated rib metastasis was being treated with zoledronic acid. Despite a successful intramedullary nail fixation and a healed fracture, 5 months later, he developed another fracture in the same femur in the subtrochanteric area. This case report delves into the intricate pathogenesis of BP-induced atypical femoral fractures (AFF) and explores the potential role of bioactive collagen peptides in their pathogenesis.

**Conclusion:** Significant challenges exist in diagnosing and managing BP-induced AFFs. Using anabolic agents and bioactive collagen peptides is a successful therapeutic intervention for these patients.

**Keywords:** Collagen peptides, nutraceuticals, osteoporosis, bisphosphonate-induced atypical fractures.

## Introduction

Osteoporosis is characterized by bone loss and microarchitectural deterioration. It is one of the most disabling consequences of aging. [1] Bisphosphonates (BPs) have been extensively recommended as the first-line therapy for osteoporosis in men and women since the 1990s. Their ability to prevent bone resorption accounts for their efficacy in treating osteoporosis and other ailments [1, 2, 3, 4]; BPs exert their pharmacological action by binding to hydroxyapatite, thereby influencing the osteoclast function and bone remodeling processes. However, the prolonged inhibition of osteoclast activity induced by BPs may lead to pathologic manifestations, notably atypical femoral fractures [5]. Atypical femoral fractures (AFFs) are stress fractures in the lateral shaft of the femur, often caused by long-term use of antiresorptive medications, such as BPs, due to their negative effect on the collagen matrix, angiogenesis, and mineralization. Variations in hip and lower limb geometry may also contribute to AFF development, potentially influencing the location of femoral stress fractures [6].

AFFs are commonly treated surgically with internal fixations, including intramedullary nails and prophylactic nailing [7], and therapeutically with anabolic agents, such as teriparatide. Although AFFs are known to heal slowly after the initial fracture has completely healed, there have been no documented instances of patients experiencing another AFF in a distinct region of the same femur with an intact nail in situ [8,9].

[1]Department of Orthopedics, Apollo Hospitals, Hyderabad, Telangana, India, [2]Department of Medical Affairs, Universal NutriScience, Mumbai, Maharashtra, India, [3]Department of Medical Affairs, Universal NutriScience, Pharmacology, Mumbai, Maharashtra, India

**Address of Correspondence**
Dr. Manish R Garg,
Department of Medical Affairs, Universal NutriScience, Pharmacology, Mumbai, Maharashtra, India
**E-mail:** manish_rgarg@yahoo.co.in

## Case Report

A 73-year-old male patient presented with a left femoral shaft fracture after a low-energy trauma at home (Fig. 1). Clinical Examination revealed no significant swelling or ecchymosis. Medical history revealed diabetes mellitus, which was being managed with oral hypoglycemic agents, and a 3-year history of prostate carcinoma with known isolated rib metastasis. He was undergoing androgen deprivation therapy concomitantly with zoledronic acid administration every 3 months.

Further investigations did not reveal any additional skeletal metastases, and there was no evidence of metastasis at the fracture site. Given the fracture's morphology, characterized by a nearly transverse orientation with a minor medial beak, it was classified as an atypical femoral fracture (AFF). The fracture

Submitted Date: 10 Aug 2024, Review Date: 12 Sep 2024, Accepted Date: 15 Sep 2024 & Published Date: 10 Dec 2024

*Journal of Clinical Orthopaedics | Available on www.jcorth.com | DOI: https://doi.org/10.13107/jcorth.2024.v09i02.690*

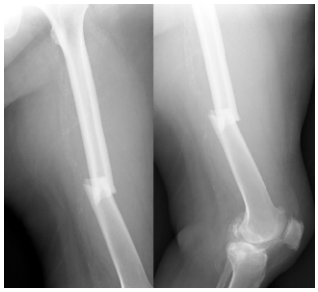

**Figure 1:** Radiograph of the left femoral shaft showing the initial atypical femoral fracture with a transverse orientation and minor medial beak, typical of bisphosphonate-related fractures.

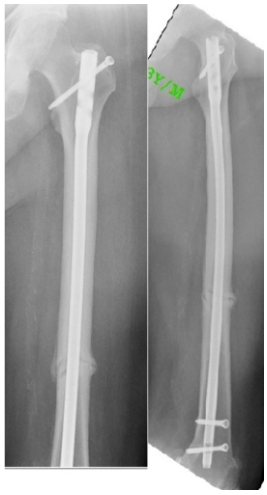

**Figure 2:** Radiographic evaluation at 5-month post-surgery demonstrated a satisfactory fracture union.

was treated by internal fixation with an intramedullary nail and proximal and distal locking screws. A radiographic evaluation at 5 months post-surgery demonstrated a satisfactory fracture union (Fig. 2). He was mobilizing with a single stick with total weight on the leg.

However, 5 months later, he presented with a gradual onset of pain in the thigh for 4 weeks, which was exacerbated after walking. Imaging studies showed a short oblique fracture at the subtrochanteric area of the femur with an intact femoral nail in situ and a very well-consolidated original shaft fracture (Fig. 3).

Since the intramedullary nail appeared to be in a satisfactory position, the new fracture was managed conservatively with bed rest for 4 weeks, followed by a gradual resumption of weight-bearing activities after 6 weeks. A 3 month follow-up radiograph demonstrated progressive healing of the second fracture (Fig 4).

## Discussion

Atypical femoral fractures (AFFs) often occur in individuals using BPs, leading to a need for surgical intervention such as intramedullary nailing [7, 10]. In this case, intramedullary nailing was performed as a therapeutic solution for the presented fracture. It is not clear how the patient developed a second fracture in the same femur with the intramedullary nail in situ. However, the same nail when left to stay in situ helped to continue to stabilize the fracture and heal it.

According to the available literature, there is a lack of documented instances where a subsequent fracture has occurred in the femur previously treated with intramedullary nailing for BP-related atypical femoral fractures (AFF). Our patient initially mobilized well, and radiographs confirmed satisfactory fracture union. However, after a low-energy trauma, the patient developed thigh pain, which was worsened on walking. Moreover, it was later diagnosed with a short oblique subtrochanteric femur fracture distant from the earlier one. The etiology of this second fracture may have a mechanical cause. However, BP's continuous path biochemical changes cannot be ruled out. While intramedullary nailing is the standard treatment for atypical femoral fractures, it has drawbacks related to BP use, including lower union rates and a high need for revision surgery (46%). Some authors reported delayed healing in up to 38% of cases, indicating prolonged recovery [11]. BPs can positively and negatively impact bone's organic matrix by altering collagen maturity and cross-linking. The bone matrix, consisting of minerals and collagen, creates a framework for calcification, which impacts both bone density and microarchitecture [12, 13]. An increase in advanced glycation end products of the extracellular bone matrix can deteriorate the mechanical properties of the bone. Research also indicates that BPs decrease angiogenesis in non-skeletal tissues; however, it can be difficult to distinguish between the suppression of osteoclastic activity and the inhibition of new vessel growth since these effects frequently co-occur [14]. However, bioactive

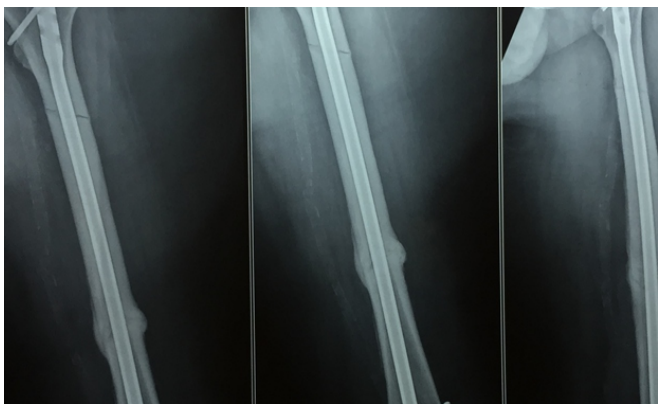

**Figure 3:** X-ray showing a short oblique fracture at the subtrochanteric area of the femur with an intact femoral nail in situ and a very well-consolidated original shaft fracture.

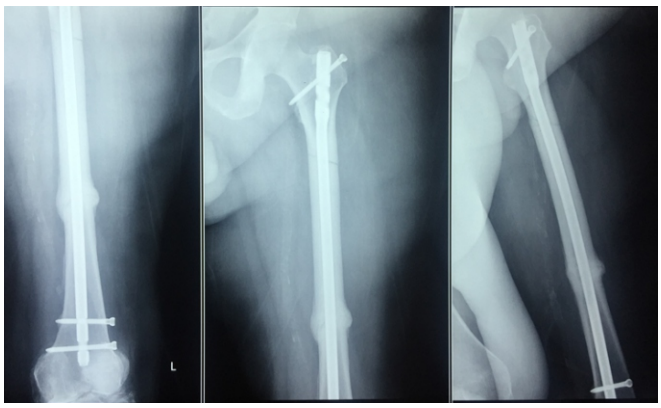

**Figure 4:** X-ray image showing early healing of the second subtrochanteric femoral fracture, 2–3 months after diagnosis and conservative management. The fracture shows signs of consolidation following a period of non-weight-bearing and gradual resumption of weight-bearing activities.

collagen peptides are known to enhance bone density and metabolism, counteracting the adverse effects of BPs and potentially reducing fracture risk [15].

Additional measures are essential for optimal patient care after surgery for an atypical fracture. Discontinuing BPs is crucial, as their continued use can impair bone remodeling and potentially delay bone healing [16, 17]. Considering the use of an anabolic agent is also highly recommended [18]. Agents, such as teriparatide and abaloparatide have demonstrated safe and effective outcomes in bone healing, especially when combined with calcium, vitamin D, and bioactive collagen peptides, improving therapeutic results [19].

Bioactive collagen peptides, being a small chain of amino acids, are readily absorbed from the gastrointestinal tract and, through the circulatory system, reach the bone marrow, where they activate the formation of osteoblast from bone marrow stem cells and inhibit the activity of osteoclast through an increase in the osteoprotegerin/receptor activator of nuclear factor kappa-B ligand ratio. Bioactive collagen peptides have been shown to enhance bone mineral density (BMD) by 4.2% in the spine and 7.7% in the femoral neck, coupled with alterations in bone turnover markers within 12 months [15]. A 4-year study on bioactive collagen peptides also showed a clinically relevant increase in BMD, with no fractures reported by any patients and no drug interaction or tolerability issues [20].

These findings highlight the need for integrating once-a-day oral bioactive collagen peptide supplementation (nutraceutical with a drug-like action) into managing AFFs and standard osteoporosis. Bioactive collagen peptides, with their dual action on both osteoblast and osteoclast (along with Calcium and vitamin D), may have a beneficial action on their own but may have synergistic action when used along with anti-resorptive (BP/denosumab) as well as anabolic (teriparatide) treatment.

## Conclusion

In summary, this case highlights that simple mechanical stabilization alone is insufficient to heal an AFF or prevent them without modifying the underlying pathobiochemical changes of the bone matrix. Hence, the management should be comprehensive, including bioactive collagen peptides, which may exert an anabolic action. Further studies involving more cases using such nutraceuticals are necessary to confirm their potential benefit.

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

**Conflict of Interest:** NIL; **Source of Support:** NIL

## References

1. Black DM, Geiger EJ, Eastell R, Vittinghoff E, Li BH, Ryan DS, et al. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. N Engl J Med 2020;383:743-53.
2. Lindsay R, Cosman F. Osteoporosis. In: Jameson JL, Fauci AS, Kasper DL, Hauser ST, Longo DL, Loscazo J, editors. Harrison's Principles of Internal Medicine. 20th ed., Vol. 2. New York: McGraw Hill; 2018. p. 2942-59.
3. Rogers MJ, Watts DJ, Russell RG. Overview of bisphosphonates. Cancer 1997;80:1652-60.
4. Ganesan K, Goyal A, Roane D. Bisphosphonate. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2024.
5. Rudran B, Super J, Jandoo R, Babu V, Nathan S, Ibrahim E, et al. Current concepts in the management of bisphosphonate associated atypical femoral fractures. World J Orthop 2021;12:660-71.
6. Tile L, Cheung AM. Atypical femur fractures: Current understanding and approach to management. Ther Adv Musculoskelet Dis 2020;12:1759720X20916983.
7. Larsen MS, Schmal H. The enigma of atypical femoral fractures: A summary of current knowledge. EFORT Open Rev 2018;3:494-500.
8. Githens M, Garner MR, Firoozabadi R. Surgical management of atypical femur fractures associated with bisphosphonate therapy. J Am Acad Orthop Surg 2018;26:864-71.
9. Giusti A, Hamdy NA, Papapoulos SE. Atypical fractures of the femur and bisphosphonate therapy: A systematic review of case/case series studies. Bone 2010;47:169-80.
10. Yoon RS, Beebe KS, Benevenia J. Prophylactic bilateral intramedullary femoral nails for bisphosphonate-associated signs of impending subtrochanteric hip fracture. Orthopedics 2010;33:267-70.
11. Pearce O, Edwards T, Al-Hourani K, Kelly M, Riddick A. Evaluation and management of atypical femoral fractures: An

update of current knowledge. Eur J Orthop Surg Traumatol 2021;31:825-40.

12. Liberman UA, Weiss SR, Bröll J, Minne HW, Quan H, Bell NH, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995;333:1437-44.
13. Adam M, Spacek P, Hulejova H, Galianova A, Blahos J. Postmenopausal osteoporosis. Treatment with calcitonin and a diet rich in collagen proteins. Cas Lek Cesk 1996;135:74-8.
14. Im GI, Jeong SH. Pathogenesis, management and prevention of atypical femoral fractures. J Bone Metab 2015;22:1-8.
15. König D, Oesser S, Scharla S, Zdzieblik D, Gollhofer A. Specific collagen peptides improve bone mineral density and bone markers in postmenopausal women-a randomized controlled study. Nutrients 2018;10:97.
16. Schneider JP, Hinshaw WB, Su C, Solow P. Atypical femur fractures: 81 individual personal histories. J Clin Endocrinol Metab 2012;97:4324-8.
17. Lin TL, Wang SJ, Fong YC, Hsu CJ, Hsu HC, Tsai CH. Discontinuation of alendronate and administration of bone-forming agents after surgical nailing may promote union of atypical femoral fractures in patients on long-term alendronate therapy. BMC Res Notes 2013;6:11.
18. Miyakoshi N, Aizawa T, Sasaki S, Ando S, Maekawa S, Aonuma H, et al. Healing of bisphosphonate-associated atypical femoral fractures in patients with osteoporosis: A comparison between treatment with and without teriparatide. J Bone Miner Metab 2014;33:553-9.
19. Gao J, Liu X, Wu X, Li X, Liu J, Li M. A brief review and clinical evidences of teriparatide therapy for atypical femoral fractures associated with long-term bisphosphonate treatment. Front Surg 2023;9:1063170.
20. Zdzieblik D, Oesser S, König D. Specific bioactive collagen peptides in osteopenia and osteoporosis: Long-term observation in postmenopausal women. J Bone Metab 2021;28:207-13.

Conflict of Interest: NIL
Source of Support: NIL

How to Cite this Article

Nallamilli SR, Althuri MK, Patwal S, Garg MR. Bisphosphonate-Induced Atypical Femoral Fractures: Pathogenesis Insights and the Role of Bioactive Collagen Peptides – A Case Report. Journal of Clinical Orthopaedics July-December 2024;9(2):118-121.