# Atypical Tibial Fracture in a 63-Year-Old Woman With Intermittent Use of Bisphosphonate Unmasking Hypophosphatasia

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We report an unusual case of atypical proximal tibial stress fracture (APTF) associated with intermittent use of bisphosphonates (BPs) and persistently low serum alkaline phosphatase (ALP) levels. We describe the case of a 63-year-old white woman who had experienced an APTF after 4 years of intermittent exposure to alendronate given for recurrent metatarsal stress fractures. BP administration was stopped after the diagnosis of the APTF. A review of her previous serum ALP levels revealed they had been consistently low. Adult hypophosphatasia (HPP) was diagnosed by the low serum ALP activity and elevated urine phosphoethanolamine levels. She was treated conservatively with analgesics. Adult HPP is an underrecognized condition associated with atypical insufficiency fractures, and BP use compounds this risk. To the best of our knowledge, we report the first case of intermittent BP exposure preceding an APTF in an adult patient with HPP, highlighting the uncommon site of the proximal tibia for BP-associated atypical insufficiency fractures, the need to screen for HPP in those with persistently low ALP levels before they begin BP therapy, and the importance of avoiding BP use in those with HPP.



**Freeform/Key Words:** hypophosphatasia, intermittent bisphosphonates, atypical tibial fracture

Hypophosphatasia (HPP) is a rare inherited disorder characterized by low serum ALP activity and defective bone mineralization [1]. Atypical femoral fractures (AFFs) have been reported in adult patients with HPP, both with and without longstanding use of bisphosphonates (BPs) [2, 3]. To the best of our knowledge, we report the first case of a patient with HPP presenting with an atypical proximal tibial stress fracture (APTF), associated with intermittent/occasional use of BPs.

## 1. Case Report

A 63-year-old white woman had presented in December 2018 with a 2-week history of atraumatic pain in the right upper tibial region. She had no systemic symptoms. Her medical

Abbreviations: AFF, atypical femoral fracture; ALP, alkaline phosphatase; APTF, atypical proximal tibial stress fracture; ASBMR, American Society of Bone and Mineral Research; BP, bisphosphonate; HPP, hypophosphatasia.

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history revealed repeated left and right metatarsal stress fractures that had occurred from 2009 to 2013. Her relevant medication history showed usage of alendronate (70 mg weekly) that had begun in June 2014. However, she admitted to taking alendronate intermittently, often missing the medication for ≤11 months at a time (Table 1). She had no history of oral glucocorticoid use, and she had no dental issues. Her other medical history was pertinent for laparoscopic resection of a right adrenal aldosterone-producing adenoma in 2011. Post-operatively, her antihypertensive medications were stopped. On examination, she was in good general condition with a body mass index of 36.1 kg/m$^2$. Tenderness was present on palpation along the upper shaft of the right tibia. A conventional radiograph showed periosteal reaction with no evidence of cortical beaking or transverse (stress) fractures (Fig. 1). A technetium-99m bone scan showed increased uptake in the region of the right proximal tibial shaft (Fig. 2). The findings from a bone biopsy were consistent with a healing fracture with no evidence of malignancy or infection. Her T-scores for bone mineral density on dual-energy x-ray absorptiometry were −1.19 at the lumbar spine and −1.87 at the neck of femur. The serum carboxy-terminal collagen crosslinks and *N*-terminal propeptide of type I procollagen levels were normal at 430 ng/L (normal range, <800 ng/L) and 49 μg/L (normal range, 15 to 90 μg/L), respectively. Serum and urine protein electrophoresis did not detect a monoclonal immunoglobulin.

At the time of the fracture, her serum biochemical parameters of bone metabolism were normal: calcium, 2.38 mmol/L; phosphate, 1.32 mmol/L; ALP, 39 U/L (normal range, 30 to 115 U/L); parathyroid hormone, 5.6 pmol/L (normal range, 1.6 to 6.9 pmol/L); 25-hydroxy vitamin D, 59 nmol/L (normal range, 50 to 150 nmol/L); and estimated glomerular filtration rate, 83 mL/min. However, on reviewing her bone metabolic profile from 2009, all the parameters were unremarkable, except for her serum ALP levels, which were frequently low, ranging from 23 to 28 U/L (normal range, 30 to 115 U/L). The higher ALP level at her presentation was likely in response to her proximal tibial insufficiency fracture. The urine phosphoethanolamine level was elevated at 13 mmol/mol creatinine (normal range, <5), consistent with a diagnosis of HPP. Her serum pyridoxal 5′-phosphate (vitamin $B_6$) was, however, within the normal range at 110 nmol/L (normal range, 20 to 190 nmol/L). She was advised to stop taking the alendronate and was treated conservatively with simple analgesics, calcium carbonate, vitamin D, and nonweight-bearing with progressive, successful healing of the fracture. With resolution, her ALP and carboxy-terminal collagen crosslinks levels had gradual decreased (31 U/L and 370 ng/L, respectively). A repeat serum pyridoxal 5′-phosphate test when she was not taking vitamin $B_6$ supplements showed that the level had returned to the upper limit of normal (190 nmol/L).

## 2. Discussion

To the best of our knowledge, we report the first case of APTF in a patient with adult HPP who had been using only intermittent BP. Our report is unique regarding the location of the fracture and that, unlike previously reported cases of AFFs in patients with HPP and long-term regular exposure to BP [2], our patient was taking the BP only occasionally. In our patient, the serum ALP levels had been previously low, although not recognized by the

**Table 1. Prescription Record Indicating Occasional Use of Alendronate From 2014 to Fracture in December 2018**

| Date of Prescription | Expected Date of Repeat Prescription | Actual Date of Repeat Prescription | Estimated Period Without Treatment, mo |
|---|---|---|---|
| 23/6/2014 | 23/12/2014 | 11/6/2015 | 6 |
| 11/6/2015 | 11/12/2015 | 19/11/2016 | 11 |
| 19/11/2016 | 19/5/2017 | 14/2/2018 | 9 |
| 14/2/2018 | 14/8/2018 | 10/12/2018 | 4 |

The patient had been without treatment for ≤30 mo.

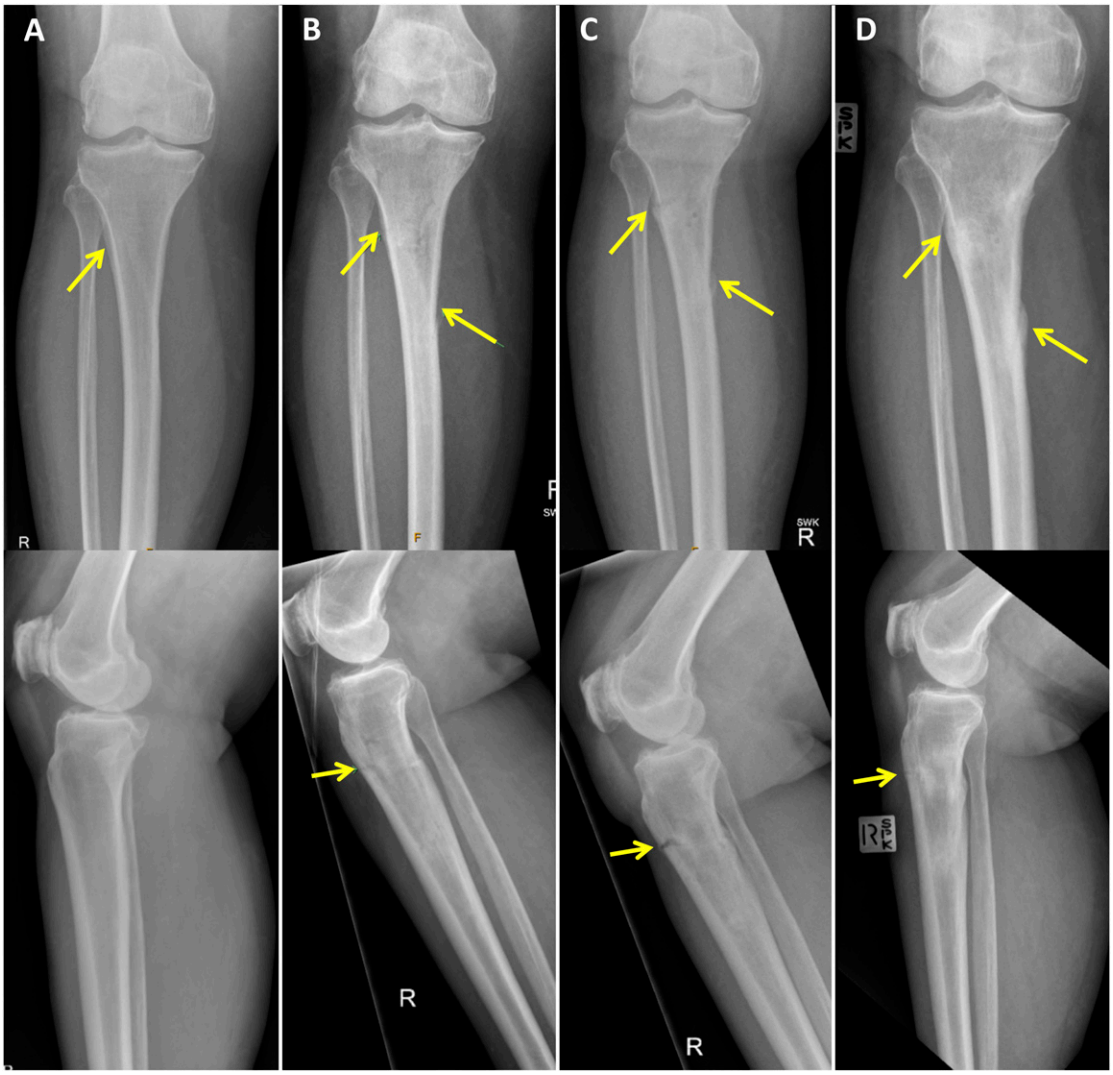


**Figure 1.** Radiographs showing evolution of APTF in HPP. (A) Radiograph at her initial presentation with pain showing only periosteal reaction along the proximal tibial shaft. (B) Radiograph 1 mo later showing a nondisplaced pathological fracture through the proximal tibial shaft and extending inferiorly through the metaphysis (*arrows*) with periosteal reaction in the lateral tibial cortex. (C) Radiograph 2 mo after presentation showing a more conspicuous fracture line, with evidence of early callus formation. (D) Radiograph 6 mo after fracture showing bony union with mature callus.

treating physicians. The primary clinical utility of ALP is that elevated levels are used to diagnose bone diseases associated with high bone turnover, such as osteomalacia and Paget disease. Little attention has been given to low ALP values [1, 4]. The clinical features of adult HPP include a propensity to fracture, the early loss of deciduous teeth, and the presence of musculoskeletal pain [1]. A spectrum of disease severity in HPP exists that is inversely related to the age of symptom onset (categorized into five forms according to symptom onset), ranging from in utero fetal death with perinatal HPP to adult HPP. Odontohypophosphatasia is the mildest variant (isolated early shedding of deciduous teeth) [5]. The disease is caused by loss-of-function mutations in the tissue nonspecific ALP gene. More than 300 mutations have been identified, with both autosomal dominant and autosomal recessive inheritance patterns [5]. The low ALP activity results in extracellular accumulation of inorganic pyrophosphate, a potent inhibitor of hydroxyapatite formation and, thus, bone mineralization. BPs are structurally similar to inorganic pyrophosphate, with earlier nonamino agents (*e.g.,* etidronate)

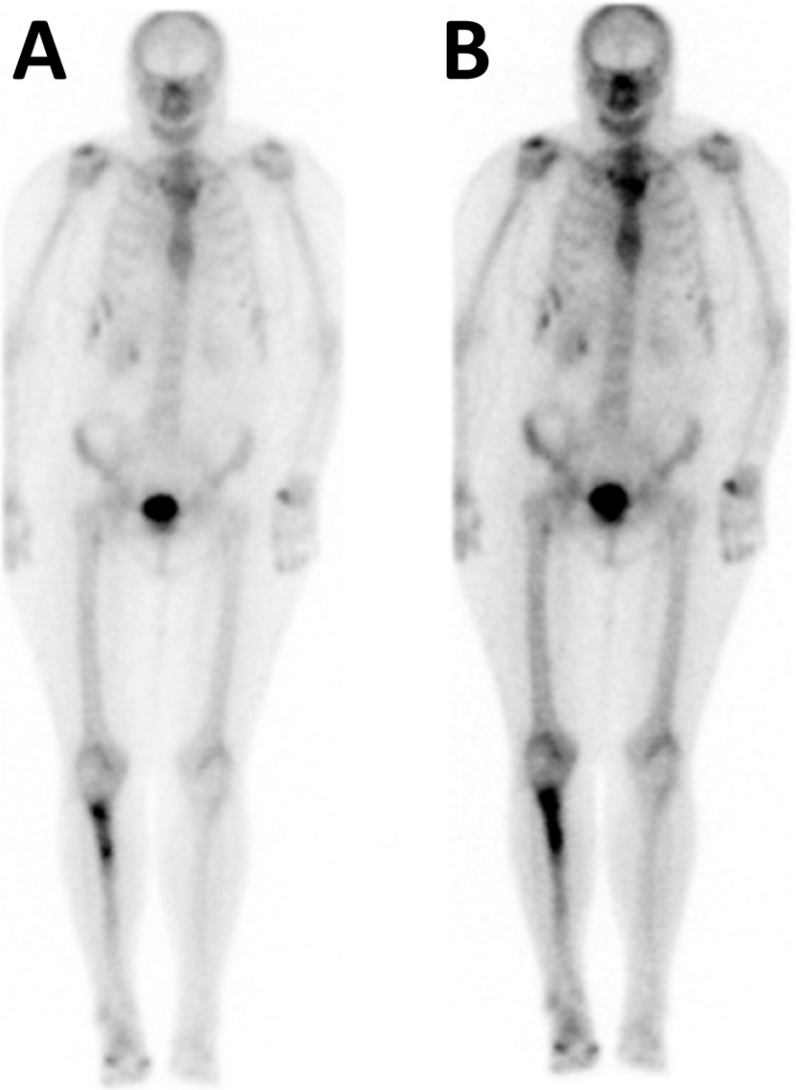


**Figure 2.** Technetium-99m bone scan showing (A) prompt perfusion and (B) hyperemia in the region of the right proximal tibial shaft.

shown to inhibit bone mineralization through a similar mechanism with toxicity presenting similar to that of HPP [2, 6, 7]. Newer agents are thought to inhibit bone remodeling through alternative mechanisms [6].

AFFs were first recognized as a rare complication of BP treatment in 2005, and the American Society of Bone and Mineral Research (ASBMR) released a position statement on AFF in 2010 that was revised in 2014 [8]. The pathogenesis has not been fully elucidated. However, these fractures share features with stress and insufficiency fractures in which accumulated, unrepaired microtrauma leads to fracture, suggesting AFFs might be related to an inability to remodel and heal the damage after prolonged usage of BPs [9]. The ASBMR taskforce on AFF reported a case definition that clearly delineates AFF from other minimal-trauma subtrochanteric fractures; it does not make reference to nonfemoral fractures [8]. Nevertheless, fractures with similar morphology at other sites, including the proximal tibia, have infrequently been reported with BP use and have been postulated to have the same pathophysiology [9–11]. Patients with severe HPP are known to sustain AFFs [12]. Furthermore, case reports have described AFFs in patients with HPP taking BPs (Table 2) [2, 13–15]. A further mechanism of insufficiency fractures in patients with HPP taking BPs has

**Table 2. Previous Reported Cases of Atypical Fractures in Patients With Hypophosphatasia Taking Bisphosphonates**

| Investigator | Fracture Site | Bisphosphonate | Interval From BP Start to Fracture, y | Genetic Confirmation |
|---|---|---|---|---|
| Sutton *et al.* [2] | AFF | Alendronate (2.5 y), zoledronic acid (1.5 y; 2 doses) | 4 | Yes |
| Righetti *et al.* [13] | Bilateral AFF | Alendronate | 10 | Yes |
| Doshi *et al.* [14] | Bilateral incomplete AFF | Risedronate | 2.5[a] | No |
| Peris *et al.* [15] | AFF | Alendronate | 8 | Yes |

[a]An incomplete fracture was present before the patient had begun BP therapy, with progression occurring with medication use.

only recently been proposed. BPs, which are analogs of calcium pyrophosphate, could inhibit the already reduced activity of ALP by binding to $Zn^{2+}$ and $Mg^{2+}$; both are needed for ALP activity [2]. The combination of defective bone mineralization and pharmacologically impaired remodeling in these patients likely precipitates these fractures. Therefore, BPs would be especially contraindicated for patients with HPP, demonstrating the importance of screening for HPP before prescribing BPs to minimize the risk of insufficiency fractures.

Adult HPP can be easily overlooked, because patients typically present with recurrent, poorly healing metatarsal stress fractures [1]. Adult HPP should be suspected especially in patients with a diagnosis of osteoporosis and low serum ALP levels before they started taking BPs, after the exclusion of other causes of hypophosphatasemia [5]. Additional biochemical evidence to support a diagnosis of HPP includes elevated levels of ALP substrates (*i.e.,* plasma pyridoxal 5′-phosphate, plasma or urine phosphoethanolamine, and plasma or urinary inorganic pyrophosphate) [2]. The single finding of a low serum ALP level alone is insufficient to diagnose HPP and, thus, requires confirmation by measuring the substrates of this enzyme and, where available, mutational analysis of the tissue nonspecific ALP gene [5]. In our patient, the serial serum ALP levels were consistently low, along with an elevated urinary level of phosphoethanolamine and high to normal pyridoxal 5′-phosphate. Our finding is in keeping with the report by McKiernan *et al.* [16], which showed 61% of those with HPP with low serum ALP levels having elevation of only one ALP substrate, either phosphoethanolamine or pyridoxal 5′-phosphate, at diagnosis. A urinary inorganic pyrophosphate level would be helpful additional information. Although essential to confirm the diagnosis, genetic studies were not conducted for our patient. Neither of these tests are readily available in Australia. The findings from the biochemical studies and the history of recurrent metatarsal stress fractures in our patient were suggestive of a diagnosis of adult HPP [1].

The incidence of mild vs moderate forms of HPP in the adult population is thought to be high, with an estimated prevalence of carriers of mild to moderate mutations of 1 in 6370 in the European population [7]. The prevalence of asymptomatic HPP carriers could even be as great as 1 in 250 to 300 persons [7]. These data indicate the need to consider an assessment for HPP for patients presenting with minimal trauma or stress fractures, especially when evaluating antiosteoporotic treatment with BP. Similar to our study, Sutton *et al.* [2] reported the case of a patient with HPP initially misdiagnosed with osteoporosis, who had developed a bilateral AFF after 4 years of treatment with BPs. Osteoporosis had also been initially misdiagnosed in our patient after recurrent bilateral metatarsal fractures and treatment with oral BPs. She had developed the fracture after 4 years of intermittent BP treatment. The ASMBR definition for atypical insufficiency fractures is limited to the subtrochanteric femur and diaphysis [8]. Except for the location in the proximal tibia, some of the ASBMR criteria were evident in our patient, including a noncommunuted tibial fracture after no trauma, prodromal pain for several weeks leading up to the fracture, and delayed fracture healing.

Involvement of a nonfemoral site highlights the risk in other weight-bearing bones and calls for broadening the definition of "atypical fractures" [8, 9].

In conclusion, HPP is a relatively common, infrequently recognized, entity that is often misdiagnosed as osteoporosis. The diagnosis of HPP should be suspected in those with a low serum ALP level before BP treatment and should be excluded as a cause of minimal trauma fractures. BP treatment should be avoided, owing to the increased risk of atypical fractures (not only AFFs). The findings from the present case have highlighted these salient practice points. Further studies are needed to elucidate the pathophysiology of atypical fractures.

## Additional Information

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***Data Availability:*** All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

**References and Notes**

1. Berkseth KE, Tebben PJ, Drake MT, Hefferan TE, Jewison DE, Wermers RA. Clinical spectrum of hypophosphatasia diagnosed in adults. *Bone*. 2013;**54**(1):21–27.
2. Sutton RA, Mumm S, Coburn SP, Ericson KL, Whyte MP. "Atypical femoral fractures" during bisphosphonate exposure in adult hypophosphatasia. *J Bone Miner Res*. 2012;**27**(5):987–994.
3. Maman E, Briot K, Roux C. Atypical femoral fracture in a 51-year-old woman: revealing a hypophosphatasia. *Joint Bone Spine*. 2016;**83**(3):346–348.
4. Maman E, Borderie D, Roux C, Briot K. Absence of recognition of low alkaline phosphatase level in a tertiary care hospital. *Osteoporos Int*. 2016;**27**(3):1251–1254.
5. Whyte MP. Hypophosphatasia—aetiology, nosology, pathogenesis, diagnosis and treatment. *Nat Rev Endocrinol*. 2016;**12**(4):233–246.
6. Fleisch H. Development of bisphosphonates. *Breast Cancer Res*. 2002;**4**(1):30–34.
7. Whyte MP. Hypophosphatasia: enzyme replacement therapy brings new opportunities and new challenges. *J Bone Miner Res*. 2017;**32**(4):667–675.
8. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster DW, Ebeling PR, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Lane JM, McKiernan F, McKinney R, Ng A, Nieves J, O'Keefe R, Papapoulos S, Howe TS, van der Meulen MC, Weinstein RS, Whyte MP. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2014;**29**(1):1–23.
9. Black DM, Abrahamsen B, Bouxsein ML, Einhorn T, Napoli N. Atypical femur fractures: review of epidemiology, relationship to bisphosphonates, prevention, and clinical management. *Endocr Rev*. 2019;**40**(2):333–368.
10. Breglia MD, Carter JD. Atypical insufficiency fracture of the tibia associated with long-term bisphosphonate therapy. *J Clin Rheumatol*. 2010;**16**(2):76–78.
11. Tan J, Sano H, Poole K. Antiresorptive-associated spontaneous fractures of both tibiae, followed by an atypical femur fracture during the sequential treatment with alendronate, denosumab then teriparatide. *BMJ Case Rep*. 2019;**12**(7):e229366.
12. Bhattacharyya T, Jha S, Wang H, Kastner DL, Remmers EF. Hypophosphatasia and the risk of atypical femur fractures: a case-control study. *BMC Musculoskelet Disord*. 2016;**17**(1):332.
13. Righetti M, Wach J, Desmarchelier R, Coury F. Teriparatide treatment in an adult patient with hypophosphatasia exposed to bisphosphonate and revealed by bilateral atypical fractures. *Joint Bone Spine*. 2018;**85**(3):365–367.
14. Doshi KB, Hamrahian AH, Licata AA. Teriparatide treatment in adult hypophosphatasia in a patient exposed to bisphosphonate: a case report. *Clin Cases Miner Bone Metab*. 2009;**6**(3):266–269.
15. Peris P, González-Roca E, Rodríguez-García SC, Del Mar López-Cobo M, Monegal A, Guañabens N. Incidence of mutations in the *ALPL*, *GGPS1*, and *CYP1A1* genes in patients with atypical femoral fractures. *JBMR Plus*. 2018;**3**(1):29–36.
16. McKiernan FE, Dong J, Berg RL, Scotty E, Mundt P, Larson L, Rai I. Mutational and biochemical findings in adults with persistent hypophosphatasemia. *Osteoporos Int*. 2017;**28**(8):2343–2348.