

Osteoporosis and Its Complications



Matthew A. Varacallo, MD*, Ed J. Fox, MD

KEYWORDS

- Osteoporosis • Fragility fractures • Vertebral compression fractures • Hip fractures
- Bisphosphonates

KEY POINTS

- At least 10 million individuals in the United States are diagnosed with osteoporosis, and more than half of the United States population older than 50 years has low bone density.
- The 2 most devastating orthopedic complications of osteoporosis are the hip fracture and the vertebral compression fracture.
- Osteoporosis is underdiagnosed in the outpatient setting, resulting in an increased rate of fragility fractures.
- There is a demonstrated overall benefit and decreased fracture risk for patients with osteoporosis who are placed on 3 to 5 years of bisphosphonate therapy.

OSTEOPOROSIS: THE BIG PICTURE

Osteoporosis is a condition in which there is compromised bone strength caused by deterioration in bone mass and quality.¹⁻⁴ Consequently, it is predominantly a condition found in the elderly, with 10 million individuals currently diagnosed in the United States.⁵ It is estimated that more than 3 times as many individuals have low bone mass and are at risk for the disease.⁵ This figure equates to more than half of the United States population older than 50 years.⁶ The common manifestation of osteoporosis is the fragility fracture. Roughly 2 million osteoporotic fractures occur each year in the United States.² This number is of great concern, considering that those who sustain such fractures increase their chance of having a future fracture by 3- to 4-fold.^{5,7} In fact, future fracture risk in the elderly may increase by up to 9.5-fold.⁸ For the average 50-year-old Caucasian woman sustaining a fragility fracture, a 40% lifetime risk for a repeat fragility fracture is inherited.¹

Osteoporosis and fragility fractures significantly compromise patients' quality of life and financially devastate the health care system. In 2005, the direct cost of fragility fractures was \$19 billion; a compilation of 2.5 million medical office visits, 430,000

Penn State Hershey Department of Orthopaedics and Rehabilitation, College of Medicine, 30 Hope Drive, Building A, Hershey, PA 17033, USA

* Corresponding author.

E-mail address: Matt.varacallo@tenethealth.com

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hospital admissions, and 180,000 nursing home admissions.^{5,9} Studies suggest that about 22% of patients move to nursing home care within 1 year of their fragility fracture.¹⁰ By 2025, the osteoporosis burden in the United States is expected to grow by nearly 50%, culminating in excess of 3 million fractures and \$25.3 billion each year in direct and indirect costs.⁹ Despite this obvious burden, current literature demonstrates that there is a significant care gap with respect to diagnosis, treatment, and management of osteoporosis. In fact, rates of follow-up care received by patients experiencing fragility fractures are reported to be anywhere in the range of 1% to 25%.^{1,3,5,8,11–20}

FRAGILITY FRACTURES

A fragility fracture is defined as a fracture that occurs as a result of a low-energy force that is insufficient to break normal bone.^{2,21} The most common locations for these fractures are the spine, hip, pelvis, proximal humerus, forearm, and wrist.²¹ Current estimates state that for the average Caucasian woman older than 50, the lifetime risk of a fragility fracture ranges from 33% to 45%.^{1,2,21} The incidence of these fractures increases dramatically in persons older than 65.² This fact is particularly concerning given that in the year 2040, the worldwide population of individuals in this age bracket is predicted to increase from 37.1 million to 77.2 million.²² Thus, a diagnostic protocol that identifies these high-risk patients before they fracture is invaluable. Depending on fracture location and patient characteristics, fragility fractures can present as either acute, debilitating events or as part of a chronic, subtle course eventually leading to a patient's inability to carry out activities of daily living.

Hip Fractures

Hip fractures remain the most serious fragility fractures in terms of morbidity and mortality; about half of these individuals never regain their previous functional capacity.²³ One-year mortality rates are estimated to be in the range of 14% to 36%.^{22,23}

Hip fractures in patients with osteoporosis often result from a fall (**Fig. 1**).² The nature of the fall must be determined, as these patients often have multiple medical comorbidities; possible causes of the fall, such as stroke, myocardial infarction, or dehydration, must be delineated because circumstances have an impact on medical optimization for surgery. One must also question a history of metastases. Patients often present with groin pain and/or pain with hip motion.² Depending on fracture pattern and degree of displacement, the leg will be shortened and rotated.²

In general, hip fractures devastate patients' quality of life and place a huge financial burden on the health care system. Most these fractures occur in women 65 years of age or older²² with or without a current diagnosis of osteoporosis. The total cost of a hip fracture is estimated to be about \$40,000 for both acute and chronic care.²³ At present, 330,000 hip fractures occur yearly in the United States.² Projected future estimates on the impact of hip fractures on the health care system are staggering. In the United States alone there are expected to be at least 550,000 hip fractures by 2040, culminating in \$62 billion in costs.² By 2050, when 1 in every 5 individuals will be older than 60, the World Health Organization (WHO) estimates that 6 million hips will be fractured each year worldwide,²⁴ a striking increase considering that in 1992 there were 1.7 million hip fractures.²⁵

Vertebral Compression Fractures

Vertebral compression fractures (VCFs) are very common in patients with osteoporosis (**Fig. 2**). Most cases occur in asymptomatic patients.²⁶ Reports estimate that

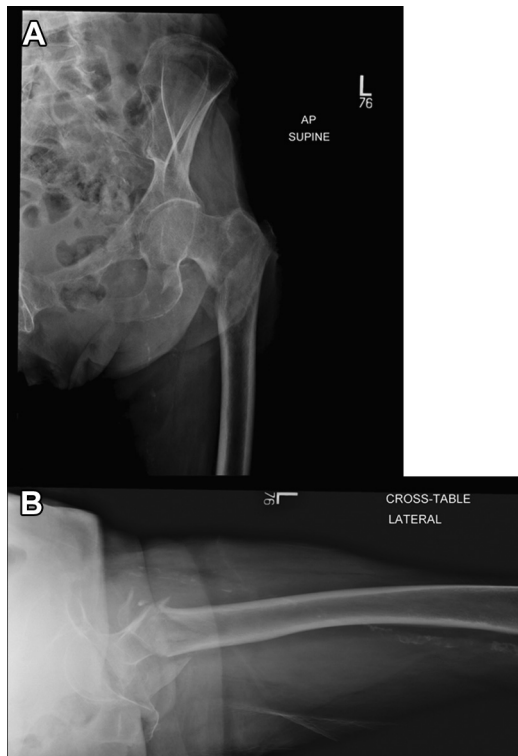


Fig. 1. Anteroposterior (AP) (A) and lateral (B) radiographs of the left hip, showing a hip fracture in a 94-year-old woman with a history of osteoporosis.

anywhere from 750,000 to 1.5 million VCFs occur yearly in the United States,^{2,27} approximately 85% of which are linked to osteoporosis.²⁸ In severe osteoporosis, the cortical and trabecular bone of the vertebral body weakens to the point where simple activities such as changing postural positions, lifting light objects, or even sneezing can cause a break in the bone.^{2,26} It has been suggested that about 30% of VCFs in patients with severe osteoporosis occur while the patient is in bed.²⁷ Regardless of the mechanism, the theory behind the increased load across the vertebral bodies is due to contraction of the paraspinal muscles.²⁷ When patients younger than 55 years present with a VCF in the absence of severe trauma, underlying malignancy must be considered.²⁷

When symptomatic, a patient with a VCF experiences acute onset of back pain with or without radiculopathy. A list of common symptoms related to VCFs is provided in **Table 1**. However, most patients will either be asymptomatic or will initially overlook the acute symptoms; this is especially true when there is minimal or no pain in the absence of neurologic complications.²⁶ The chronic and subtle course often turns out to be a debilitating condition that severely limits function.^{2,26} VCFs can lead to segmental instability when the vertebral body collapse is greater than 50% of the initial height.²⁷ Some compression fractures propagate from the initial microfracture in the anterior column of the vertebra, and result in wedging. Others may be due to a larger force of impact and result in failure of the trabeculae, which causes initial collapse of the entire vertebral body.² Subsequently the segmental instability increases the load

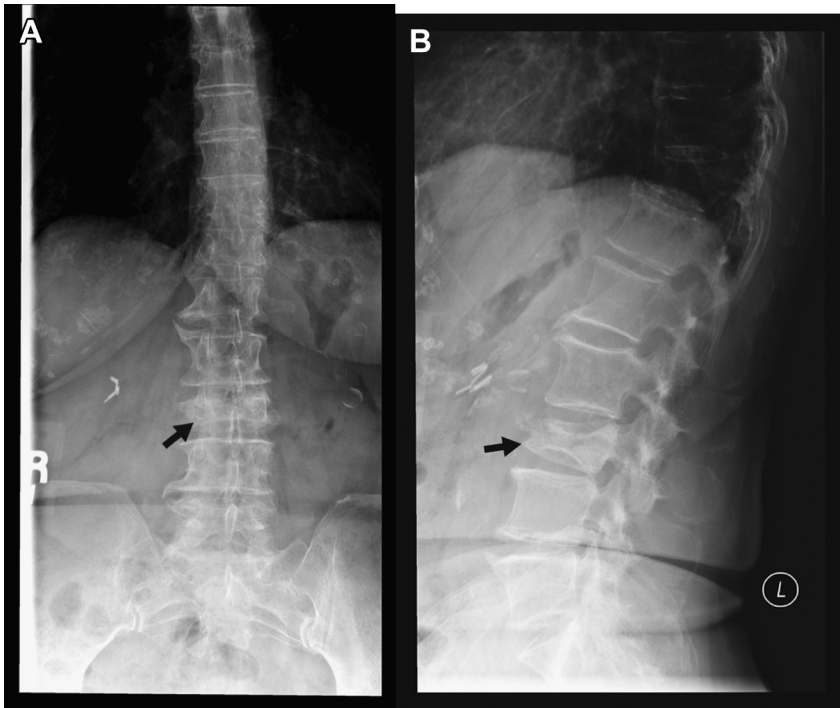


Fig. 2. AP (A) and lateral (B) radiographs of the lumbar spine, showing an L3 vertebral compression fracture in an 86-year-old woman with a history of osteoporosis.

on adjacent levels. One study suggested that regardless of an individual's bone mineral density (BMD), having 1 VCF increases the risk of a subsequent VCF by 5-fold.²⁷ Over time, as the kyphotic deformity worsens, contraction of the paraspinal muscles to maintain posture continuously increases the load across the vertebral bodies, and subsequent VCFs occur even after the initial one has healed.²⁷ This process perpetuates an unfortunate cycle as kyphotic deformity worsens and progressively limits

Table 1 Common presenting symptoms and complications of vertebral compression fracture	
Symptoms	Complications
Acute-onset back pain	Low-grade back pain
Back pain increases on postural changes	Thoracic kyphosis and lumbar lordosis
Back pain decreases when lying on back	Decreased pulmonary function, respiratory capacity, and increased prevalence of atelectasis pneumonia
Tenderness to palpation over affected level	Gastrointestinal problems, decreased appetite, weight loss
Decreased spinal mobility secondary to pain	Disuse osteoporosis
	Deep venous thrombosis due to inactivity
	Low self-esteem and emotional, social problems

Modified from Alexandru D, So W. Evaluation and management of vertebral compression fractures. *Perm J* 2012;16:46–51.

function, decreases quality of life, increases future fracture risk, reduces lung function, impairs balance, and increases the incidence of falls.²⁸

DIAGNOSING OSTEOPOROSIS

Given that osteoporosis is a disease that affects the microarchitecture of bone and that routine bone biopsy is not used in clinical practice, BMD testing is the gold standard for diagnosis. One of the biggest problems that fuels this osteoporosis burden is the lack of a universally adopted BMD screening protocol. There still remains some controversy in regard of how cost-effective such a protocol can be made. The National Osteoporosis Foundation (NOF), in agreement with the US Preventive Services Task Force, recommends BMD testing for all women aged 65 years and older. In addition, the NOF recommends the following individuals for BMD testing: men aged 70 years or older, men or women 50 years or older who have had a fragility fracture, men between 50 and 70 years old with 1 or more risk factors for osteoporosis, and postmenopausal women younger than 65 years with 1 or more risk factors for osteoporosis.²⁹ Although this remains a legitimate set of recommendations, physicians must also rely on each individual's fracture-risk assessment. The WHO developed a fracture-risk algorithm (FRAX), which is an estimate of a patient's 10-year absolute hip/fragility fracture score. Some of the documented parameters include age, gender, race, body mass index, history of prior fractures, family history of fractures, medication use, and current smoking and drinking history.²³ The diagnosis of osteoporosis is often established clinically once a patient sustains a fragility fracture, and is subsequently confirmed via BMD measurements by dual-energy x-ray absorptiometry (DEXA) of the spine, hip, and/or wrist. A DEXA scan measures the central bone mass, and a patient's T score represents the standard deviation from the mean peak value in the age-matched population. The WHO set a T score less than -2.5 as diagnostic for osteoporosis, with scores between -1 and -2.5 indicating osteopenia and a score greater than -1 being normal.²⁷

ADDRESSING THE OSTEOPOROSIS CARE GAP

Barriers to Identification of Patients at Risk

In an era of chronic illnesses, the unfortunate reality is that osteoporosis is commonly overlooked in the outpatient setting. Many patients at the highest risk for osteoporosis often will have some combination of chronic conditions such as congestive heart failure, chronic obstructive pulmonary disease, diabetes, and/or dementia^{30,31}; these issues ultimately consume the entire office visit. Thus, not all patients meeting the NOF criteria for BMD testing actually receive a DEXA scan. Furthermore, even fewer are treated for their low bone density.^{8,17,23}

There is clear evidence that treatment with calcium, vitamin D, and a bisphosphonate helps prevent future fractures.⁸ Despite this common knowledge, the follow-up rates for treatment after a fragility fracture are extremely low. Some of the major barriers to diagnosis and treatment include lack of knowledge and awareness from both the physician and the patient,^{8,23} the perception by the orthopedic surgeon that the diagnosis and treatment is not his or her responsibility,⁸ low rates of referral to the appropriate osteoporosis service,¹⁷ the cost of therapy, side effects of medications, and multiple medical comorbidities.⁸ In fact, one study reported that only 27% of eligible women between 66 and 70 years of age received DEXA testing. The same study reported that only 16% of women between the ages of 81 and 85 received testing, and only 9.7% of women between 86 and 90 years of age had DEXA testing.²³ As a result, not only does the quality of life of these patients suffer but there also is a high cost associated with long-term complications.

Providing Solutions

Given the morbid nature of this condition combined with the overall financial impact on the health care system, more efficient approaches and protocols have been studied and are starting to be implemented worldwide.^{1,3,5,8,11–20} Some reports have even detailed the financial savings from fracture prevention versus the cost of implementing such programs.²³ These protocols are geared toward efficiently identifying patients at high risk for osteoporosis and improving follow-up rates in the clinic. By and large, there is a wide range of systems in place geared toward recognizing these patients both in the inpatient setting and in the outpatient arena. Although the programs differ in many ways, the underlying goals are undisputed: (1) improve the efficiency for identifying patients at risk for osteoporosis and enhance the rate of postfracture diagnosis and treatment initiation; and (2) improve patients' quality of life and relieve the financial burden of osteoporosis on the health care system.

Unfortunately, owing to the lack of a universal standardized protocol for BMD screening and the failure to address osteoporosis in the clinic, one of the more common ways to identify these high-risk patients is postfracture fracture. In many ways, these fractures serve as the initial screening protocol to identify those currently not on treatment.

Once these patients are identified, it is crucial that they are managed as efficiently as possible while in the hospital. Quick diagnosis, early medical management, surgical intervention (when necessary), and limiting the patient's stay in hospital all require a cohesive management plan that spans multiple specialties and hospital departments. Bugata and colleagues² reported excellent outcomes after implementing a "Geriatric Fracture Program" based on a comanaged care model that has become standard protocol at multiple institutions. The fracture patient is rapidly assessed in the emergency department (ED) and is admitted to the orthopedic surgery service once medically stable. The orthopedic team works in conjunction with the geriatric medicine hospitalist service to assess the candidate's current medical stability, and optimizes the patient for early surgery. Most patients are operated on within 24 hours, and postoperative care follows a standard protocol with the medicine and surgical services. The stable patient is discharged by the third day.²

Transitioning to the outpatient setting, the next step is to encourage a follow-up appointment in the clinic for BMD testing. There are reports that less than 30% of postmenopausal women and less than 10% of men with prior fragility fractures are treated for osteoporosis.¹⁹ In general, current literature cites the rate of follow-up care for all patients experiencing fragility fractures as anywhere from 1% to 25%.³ In a study by Varacallo and colleagues,³ patients at high risk for osteoporosis were identified on arrival to the ED based on ICD-9 diagnostic fracture codes. An automated protocol was developed that captured patients older than 50 years who visited the ED for a fragility fracture. These patients were sent a follow-up letter after the initial visit to the ED that advised them to follow up with a medical provider to obtain a DEXA scan and directly address his or her risk for osteoporosis. These types of programs are fiscally responsible, easy to implement, and have documented significant improvements in the follow-up rate in the outpatient setting on discharge from the hospital. Another example reported by Sugi and colleagues¹⁹ demonstrated a nearly identical protocol with similar success.

As mentioned previously, osteoporosis diagnosis and BMD testing is often overlooked in the outpatient setting. In today's age of increasing patient medical comorbidities, osteoporosis tends to fall by the wayside. Bogoch and colleagues⁸ reported the successful implementation of an Osteoporosis Exemplary Care Program

for the education, investigation, and treatment of high-risk patients. A central coordinator was hired to integrate the outpatient fracture clinic, the inpatient orthopedic unit, the metabolic bone disease clinic, and the nuclear medicine unit for the evaluation and management of patients sustaining a fragility fracture. Three hundred fifty-nine patients were identified as at high risk after the fragility fracture and more than 95% were appropriately diagnosed, treated, and referred for care. Vaile and colleagues²⁰ created a First Fracture Project with a dedicated Osteoporosis Nurse (ON). The ON attended the fracture clinic daily, and ensured that high-risk patients were educated and up-to-date on blood work and BMD testing. The ON also coordinated follow-up with the family physician. Before the intervention, less than 12% of patients were taking calcium, vitamin D, or other antiosteoporosis medications, and new treatment had been commenced in a very small percentage. Only 9% were taking calcium, 11% vitamin D, and 11% bisphosphonate. After 6 months of intervention, one-third of patients were taking calcium and/or a bisphosphonate and one-quarter were taking vitamin D.

In reality, the care for a patient at high risk of osteoporosis can be managed by many types of physicians across a wide range of specialties. If a primary care provider (PCP) is comfortable prescribing osteoporosis medications and monitoring appropriate laboratory tests and DEXA scans, the patient does not need to be seen at a specialty facility. If at any time there is doubt regarding the treatment and follow-up regimen, the patient should be referred to a specialist with an osteoporosis clinic (ie, endocrinology, rheumatology, orthopedics, obstetrics/gynecology). The patient may then be referred back to the PCP for continued follow-up.

Once the gaps that exist between recognition and treatment are bridged, patients' quality of life will improve and the health care system will experience less financial burden; in fact this has already been demonstrated on an institution-by-institution level. For example, Kaiser Permanente's Healthy Bones Program uses a closed-panel Health Maintenance Organization component that has demonstrated efficiency in each of these areas.² Furthermore, automated programs are promising, given their potential to be universally adopted at any hospital.³

TREATMENT

Treatment protocols have been well established to date. On the most basic level, most adults older than 50 years should be receiving 1200 to 1500 mg of calcium per day. Most are only getting about half of this recommendation.² Although there is a modest benefit in fracture prevention associated with supplementation,³² it is important to be aware of the risk of routine calcium supplementation in certain patient subgroups. For example, calcium supplements accelerate vascular calcification and mortality in patients with renal failure, including both dialysis and predialysis individuals.³³⁻³⁵

Vitamin D is recommended at 800 to 2000 IU per day or enough to maintain a serum 25-OH vitamin D level of at least 32 ng/mL.² The amount of vitamin D required is based on diet, sunlight exposure, age, obesity, skin pigmentation, concurrent medication use, and time of year. Older adults require 2000 IU.² Several trials have shown that inadequate intake of calcium and vitamin D is an important risk factor for developing osteoporosis and experiencing fragility fractures.²¹ Patients experiencing low-energy hip fractures have demonstrated a 70% to 90% vitamin D insufficiency rate.² Vitamin D can also improve parameters beyond bone strength. One study noted its effect on balance, lower extremity muscle strength, gait speed, and performance in individuals older than 65 years.³⁶

Beyond basic supplements, there are many different categories of medications approved for the treatment of osteoporosis (Tables 2 and 3). Each category fulfills some component of maintaining bone mass, limiting bone loss, and reducing fracture risk.²

Bisphosphonates are the most commonly prescribed medication.³⁷ These agents are hydroxyapatite analogues that directly deposit into bone and interfere with osteoclast bone resorptive function, and ultimately induce their apoptosis.⁴ In 1995, alendronate became the first bisphosphonate to be approved by the Food and Drug Administration (FDA) for the treatment of osteoporosis.⁴ The Fracture Intervention Trial (FIT) reported a relative risk reduction for all fractures across all age groups,³⁸ and another found BMD measurements to improve at both the spine and hip in elderly women residing in long-term care facilities.³⁹ There is a plethora of evidence reporting that the use of bisphosphonates results in reduction of fracture risk. However, there is some variation when comparing different types of bisphosphonates, the fragility fractures they help prevent, and the patient populations for which they have demonstrated efficacy (see Table 3). For example, alendronate, risedronate, and ibandronate all reduce the incidence of vertebral fractures (see Table 3).²⁹ However, alendronate and risedronate are approved for both prevention and treatment of osteoporosis in men and postmenopausal women, and in osteoporosis secondary to excessive glucocorticoids; ibandronate is only approved for treatment in postmenopausal women (see Table 2).²⁹

Beyond bisphosphonates, selective estrogen receptor modulators are also approved for the treatment of osteoporosis; raloxifene was the first on the market. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial demonstrated a decrease in the risk of vertebral fractures.⁴⁰

Teriparatide is the lone anabolic agent. A recombinant form of parathyroid hormone (PTH), this agent primarily stimulates osteoblasts to produce bone.^{2,4} Because persistently high levels of PTH or a continuous infusion of PTH favors bone resorption,⁴¹ teriparatide is FDA-approved as a once-weekly injection for use in patients at high risk for osteoporotic fracture. Unlike bisphosphonates, the protective effects of PTH begin to

Drug	Postmenopausal Osteoporosis		Glucocorticoid-Induced Osteoporosis		Men
	Prevention	Treatment	Prevention	Treatment	
Estrogen	X				
Calcitonin (Miacalcin, Fortical)		X			
Raloxifene (Evista)	X	X			
Ibandronate (Boniva)	X	X			
Alendronate (Fosamax)	X	X		X	X
Risedronate (Actonel)	X	X	X	X	X
Zoledronate (Reclast)	X	X	X	X	X
Denosumab		X			X
Teriparatide (Forteo)		X		X	X
Risedronate (Atelvia)		X			

Modified from Diab DL, Watts NB. Diagnosis and treatment of osteoporosis in older adults. *Endocrinol Metab Clin North Am* 2013;42:305–17.

Table 3
FDA-Approved agents and evidence of fracture-risk reduction

Drug	Vertebral		
	Fracture	Nonvertebral Fracture	Hip Fracture
Calcitonin (Miacalcin, Fortical)	X	No effect demonstrated	No effect demonstrated
Raloxifene (Evista)	X	No effect demonstrated	No effect demonstrated
Ibandronate (Boniva)	X	No effect demonstrated	No effect demonstrated
Alendronate (Fosamax)	X	^a	X
Risedronate (Actonel, Atelvia)	X	X	^a
Zoledronate (Reclast)	X	X	X
Denosumab	X	X	X
Teriparatide (Forteo)	X	X	No effect demonstrated

^a Evidence for effect, but not currently an FDA-approved indication.

Modified from Diab DL, Watts NB. Diagnosis and treatment of osteoporosis in older adults. *Endocrinol Metab Clin North Am* 2013;42:305–17.

decline shortly after discontinuation of therapy, and use of the former before use of the latter has been demonstrated to delay the anabolic response of teriparatide. However, currently it remains difficult to obtain insurance coverage for teriparatide until a treatment course of bisphosphonates is attempted.⁴²

BISPHOSPHONATE COMPLICATIONS AND THE ATYPICAL FEMUR FRACTURE

Bisphosphonates directly inhibit osteoclast function and halt bone turnover.⁴³ As with any medication, there is an inherent risk of side effects. Two major clinical side effects related to bisphosphonate therapy are osteonecrosis of the jaw and the atypical femur fracture. Although a detailed review of the former is beyond the scope of this discussion, bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a rare yet devastating complication first reported in the literature in 2003.⁴⁴ According to a systematic review of the literature by Woo and colleagues,⁴⁴ the most important predisposing risk factors for developing BRONJ are the type, dose, and route of administration of the bisphosphonate, and a history of trauma, dental surgery, or dental infection. Ninety-four percent of cases involved intravenous administration of primarily pamidronate and zoledronic acid. Furthermore, 85% of patients were receiving high-dose therapy for multiple myeloma or metastatic breast cancer. The dosing for oncologic indications is up to 12 times higher than doses used for osteoporosis. The oral lesions associated with BRONJ were documented as early as 4 months and up to 39 months after treatment induction.

Bisphosphonates have long been praised for their ability to improve BMD scores and reduce the risk for fragility fracture.⁴⁵ However, safety and efficacy have only been rigorously evaluated in short-term studies over a 3- to 5-year time period.⁴³ Beyond 5 years, the evidence for benefit against nonvertebral fractures is limited; recent literature has highlighted reports of atypical femur fractures with prolonged bisphosphonate therapy. This finding is thought to be related to severely suppressed bone turnover rates and decreased mineralization.³⁷ In normal bone physiology, cyclic loading leads to the accumulation of microdamage in bone. Such microdamage normally would stimulate bone remodeling. Prolonged suppression of bone turnover via bisphosphonate therapy is believed to play a part in the susceptibility of these bones to fracture.⁴⁶

The femur is the only bone reported in the literature to fracture from prolonged bisphosphonate use. The classic atypical fracture affects the subtrochanteric or diaphyseal region following a low-energy trauma, and displays a distinct morphology characterized radiographically (**Fig. 3C**).^{45–47} This fracture differs from typical hip fractures found in the femoral neck, trochanteric, and intertrochanteric regions of the femur.⁶ Atypical fractures demonstrate simple transverse or oblique, noncomminuted patterns with a medial spike and lateral cortical thickening.⁴⁶ Furthermore, they often occur bilaterally, may clinically present as anterior thigh pain in the prodrome, and often lack inciting trauma (see **Fig. 3B, C**).⁴⁸ In 2009, the American Society of Bone and Mineral Research rendered a task force that reviewed all available data correlating bisphosphonate use with these fractures, and the committee decided on major and minor criteria and radiographic features that would improve the identification and characterization of these atypical femur fractures (**Box 1**).⁴⁹

Much attention should be given to the patient presenting with mild thigh discomfort while on bisphosphonates. Anterior thigh pain can be associated with a periosteal stress reaction before the fracture (see **Fig. 3B**).⁴⁶ These patients can present in the clinic weeks to months before sustaining the complete fracture (see **Fig. 3C**).⁴⁵ However, not all patients will present in this fashion, and currently there are no clinical criteria to aid the physician in early detection of fractures in asymptomatic patients.⁴⁵

Studies have shown that the incidence of atypical femur fractures while on bisphosphonate therapy is relatively low. For example, one study demonstrated an

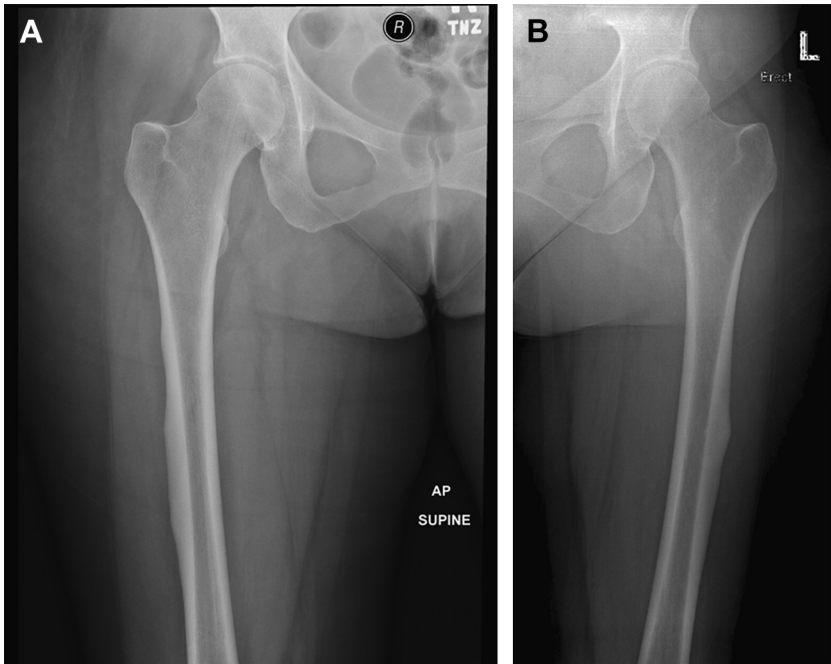


Fig. 3. AP radiographs of the right (A) and left (B) femur in a 55-year-old woman who was referred to the clinic 2 years after sustaining a fall, with continuing pain in her left leg and on bisphosphonate therapy for 10 years. The patient suffered from a bisphosphonate-induced atypical stress fracture (B), and subsequently developed an atraumatic, atypical fracture of the left femur 3 weeks later (C). She was treated with a cephalomedullary nail (D) for fracture fixation. (E) Follow-up radiograph at 1 year shows fracture healing.

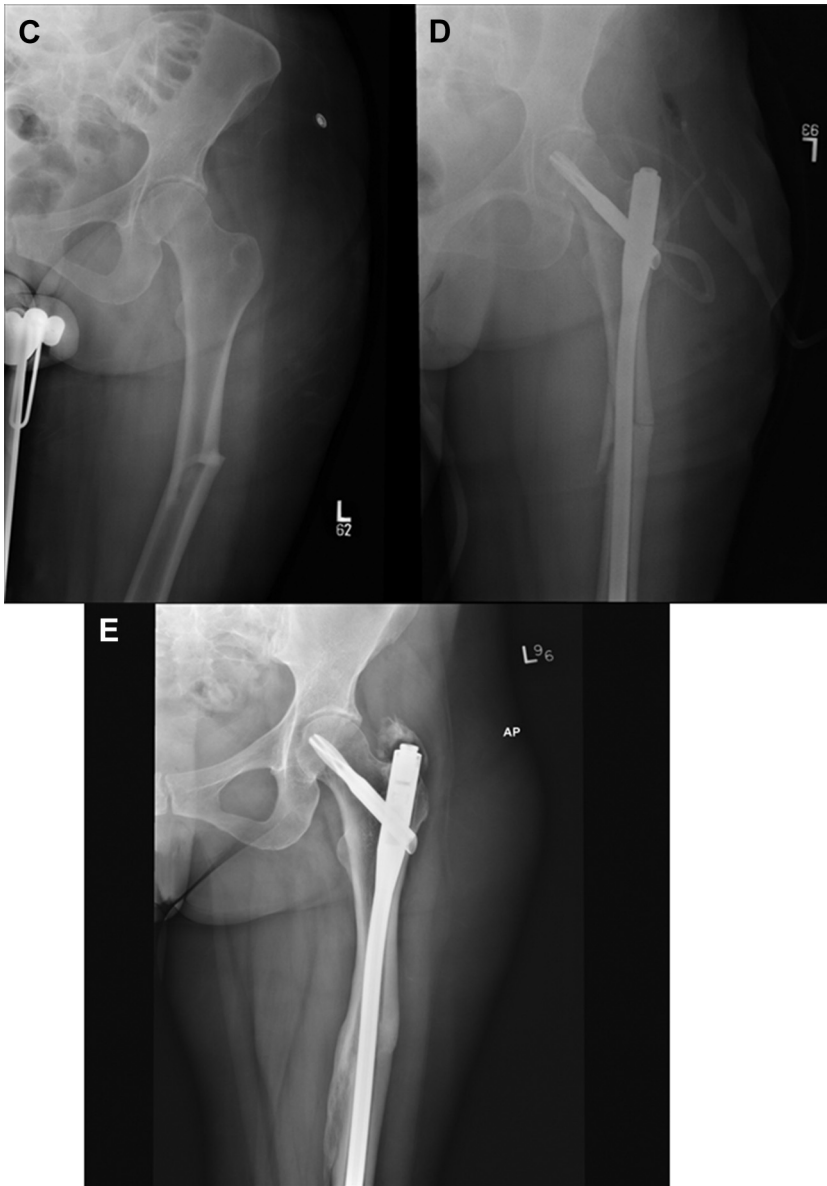


Fig. 3. (continued)

incidence of 1 per 1000 patients,⁵⁰ and another reported 0.61 fractures per 1000 patients per year. Tamminen and colleagues⁴⁷ found the combined rate of subtrochanteric or diaphyseal femur fractures in patients taking bisphosphonates to be 2.3 per 10,000 patient-years. These statistics should be analyzed alongside the expected rate of hip fractures in elderly osteoporotic patients who are not taking bisphosphonates. For example, Dell and colleagues⁴⁸ found that the age-adjusted incidence rate for atypical femur fractures was 1.78 per 100,000 per year with treatment duration

Box 1**American Society of Bone and Mineral Research major and minor criteria for atypical femoral fractures***Major features of atypical fractures*

Location: subtrochanteric and shaft

Orientation: transverse or oblique

Trauma: minimal to none

Other: medial spike when fracture is complete, absence of comminution

Minor features of atypical fractures

Cortical thickening

Periosteal reaction of lateral cortex

Prodromal pain

Bilateral, delayed healing

Concomitant drugs: bisphosphonates, steroids, proton-pump inhibitors

of up to 2 years. The incidence rate increased to 113.1 per 100,000 per year when treatment duration exceeded 8 years. Incidence of hip fracture in all women 45 years of age or older in this same study population was 224 per 100,000 per year. This study agrees with previous work analyzing the placebo arms of bisphosphonate trials with treatment durations of 3 to 4 years. Hip-fracture incidence in placebo groups was 750,³⁸ 833⁵¹ (vertebral fractures), 1390⁵² (age 70–79 years with osteoporosis), and 4200⁵² (age >80 years with osteoporosis) per 100,000 per year. Thus, hip-fracture rates are reduced by 20% to 50% with bisphosphonate therapy.

Several articles have investigated the appropriate duration of bisphosphonate treatment. As mentioned earlier, the safety and efficacy in the initial 3- to 5-year time period has been thoroughly evaluated, and there is a clear benefit in fracture reduction experienced by patients on treatment. Although no clear consensus has been reached outside of this time frame, individual risk factors such as age, race, BMD, family history, and fracture history will always play a part in the risk-to-benefit ratio. For example, individuals of Asian descent have demonstrated an increase in prevalence for atypical femur fractures.³⁷ Patients at a lower risk of fracture may not benefit beyond the initial 5 years of therapy.^{43,48}

There are situations whereby the decision to stop treatment is more straightforward. For example, a few studies have reported that there is a significant correlation between continued bisphosphonate use after an initial atypical femur fracture and a subsequent contralateral atypical femur fracture. Specifically, one study in California noted that the incidence of a contralateral atypical femur fracture was 41% in patients who continued with treatment for 3 years after the first fracture. The rate in the group that discontinued treatment after the initial fracture was 19%.⁵³ Another study demonstrated a 70% reduction in the relative risk of developing atypical femur fractures per year after bisphosphonate withdrawal.³⁶

Although the incidence of both BRONJ and atypical femur fractures is low, it should be a component of the physician's discussion with the patient in regard of initiating bisphosphonate therapy. The decision to treat should always be based on an educated and informed decision between the physician and the patient. It is imperative to remain cognizant but nonjudgmental regarding the potential for a patient's media-driven bias toward bisphosphonate complications. Education and transparency are essential.

Patients may fail to realize the true benefits of fracture-risk reduction while on treatment, compared with the rare chance of having a devastating complication while on a bisphosphonate. Each patient needs to be educated about the importance of secondary prevention of fragility fractures. Rates of patient compliance and adherence to treatment are already low,⁵⁴ and failure to address this aspect of bisphosphonate therapy may further exacerbate the communication barrier between the physician and patient that is a large component of noncompliance.

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