Evolution of Atypical Femur Fractures and the Association with Bisphosphonates

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Abstract
For almost 15 years bisphosphonates have been the mainstay of prevention and treatment of fragility fractures, particularly in post-menopausal women. As a result, there has been a decrease in fragility fractures, along with the health care costs associated with treating them. However, with all drugs, there are always concerns with side effects and potential complications. Atypical femur fractures have been observed in women taking bisphosphonates, a complication the drug was designed to prevent. There is no definitive link between bisphosphonates and atypical femur fractures and no protocol to managing these fractures. This review discusses the evolution and development of bisphosphonates and offers the latest information regarding evidence surrounding the link to atypical femur fractures.

Osteoporosis is a common disorder that affects predominantly women and is a contributing factor to approximately 1.5 million fractures per year in the USA. The majority of these fractures are hip fractures, with an estimated treatment cost of more than $10 billion. On average, a 50-year-old Caucasian woman has a risk of sustaining a hip fracture during her remaining lifetime of about 16%.1

In 1992, the World Health Organization (WHO) met with a group of osteoporosis experts to come to a consensus in the diagnosis of osteoporosis. The meeting had been organized because there was no professional opinion about how to diagnose osteoporosis. Prior to this meeting, doctors diagnosed women with osteoporosis only after a patient sustained a low energy fracture. By the early 1990s, the technology of the bone scanner had evolved where it was possible to determine how weak the bone was prior to any fracture. Therefore, the goal of the WHO meeting was to determine how to apply the medical technology to the clinical diagnosis of osteoporosis.

Given that all women after the age of 30 lose bone density, the experts sought to evaluate how much is bone loss is normal and how much bone loss should be considered a disease. Anna Tosteson, professor at Dartmouth, who attended that meeting said “Ultimately it was just a matter of ‘well the line has to be drawn somewhere’ and as I recall it was a very hot meeting room and people were in short sleeves and you know it was time to move on, if you will. And frankly I can’t remember who it was who stood up and drew the picture and said let’s do this.”2

So, in 1992 at the WHO meeting, a line was drawn through the graph with diminishing bone density and decreed every woman on one side of that line has a “disease.” This then brought about a new dilemma of categorizing women just on the other side of the line. The experts decided to use the term “osteopenia,” mostly because they thought it might be useful for public health researchers who like clean-cut categories, not with the intention of clinical diagnosis for the patient. The experts did not intend for clinicians to think of osteopenia as a disease that needed treatment.

After this meeting, clinical trials began and were very promising as they reported a significant decrease in the incidence of hip and spine fractures with a concomitant reduction in associated healthcare costs.1-3

Currently the recommended tool to diagnose osteoporosis is FRAX (Fracture Risk Assessment Tool), which is a fracture assessment tool, developed by the WHO.4-9 It divides patients by race and geographic region. It is designed

to determine whether a patient is at risk for developing a fracture in the next 10 years. However, it cannot be used if a patient is already taking bisphosphonates or has already sustained a fragility fracture.

In the early 1990s, bisphosphonates (BPs) emerged as potent drugs for the treatment of osteoporosis. In 1996, Black and coworkers published the landmark paper of the FIT (Fracture Intervention Trial), which showed that bisphosphonates effectively reduced the risk of osteoporotic fractures with relatively little side effect. Over 2,000 women were randomized to placebo or alendronate and followed for 36 months. There was a significant reduction in fragility fractures of the femoral neck, hip, and spine. The women treated in this trial were predominantly osteopenic, with an average bone density of -2.1, which was less than the -2.5 that the WHO determined to be osteoporotic. Bisphosphonates reduced a woman’s risk of a future fracture; however, the risk was not zero.

After Black’s landmark study in the 90s, there was a surge in the diagnosis of osteoporosis and treatment with bisphosphonates.

Evolution of Bisphosphonates

Bisphosphonates were first discovered by chemists in Germany in the late 1800s. Initially, they were used either as corrosion inhibitors or as complexing agents in the textile, fertilizer, or oil industries. In the 1960s, research on bisphosphonate was primarily focused on its use as a chelator for dental cavities. During this time, it was shown that pyrophosphate, a derivative of bisphosphonate, was shown to inhibit calcification of tissues by binding to hydroxapatite. However, orally administered pyrophosphates are hydrolyzed in the gut, thereby rendering them inactive. Bisphosphonates are resistant to hydrolysis and could therefore be administered orally.14

The first bisphosphonate used in humans was etidronate for myositis ossification. It was shown that bisphosphonates inhibited osteoclastic-mediated bone resorption, and this led to their use as bone protective agents.

In 1996, bisphosphonates were approved for use of treatment for osteoporosis. Merck wanted Fosamax to be its new blockbuster drug. However, it was not selling. It made 281 million dollars in 1996, and for drug company, that is considered a failure. In an effort to improve their sales, Merck hired Mr. Jeremy Allen who created the “Bone Measurement Institute,” which was comprised of just him. The Bone Measurement Institute worked to spread the DEXA machines by driving down the cost. It also lobbied congress to pass the “Bone Measurement Act,” legislation that changed Medicare reimbursement to cover bone scans. All of the organizations who lobbied for this received money from Merck. Up until now, bone scans were not covered by insurance.

Then, in 1997, the FDA approved a 5 mg dose (lower than the usual 10 mg) for osteopenia. Osteopenia went from being a “category for public health researchers” in 1992 to a condition that women believed needed medical treatment. Fosamax’s sales skyrocketed.

Mechanism of Bisphosphonates

Bisphosphonates work by inhibiting the melvalonate pathway, which is essential for osteoclast survival. There are nitrogen and non-nitrogen bisphosphonates. In general, a hydroxyl substitution at R1 enhances the affinity of bisphosphonates for calcium crystals, while the presence of a nitrogen atom in R2 enhances their potency and determines their mechanism of action. On a molecular level BP inhibits the actin rings, which allow the osteoclasts to attach to bone. It also inhibits intracellular trafficking, and as a result, osteoclasts lose the ruffled border. They are inactivated and eventually undergo apoptosis.15,16

Atypical Femur Fractures

The incidence of hip fractures is approximately 460/100,000 person years. Subtrochanteric fractures account for 7% to 10% of hip fractures, and atypical femur fractures are even rarer.17 Subtrochanteric fractures are typically the result of a high energy mechanisms and not a fall from a height like most hip fractures. The morbidity and mortality are similar to femoral neck or intertrochanteric fractures. Less than half of patients with this fracture who are treated surgically return to their pre-function state.

Typical femur fractures are the result of high-energy mechanism, and the typical femur radiographic fracture pattern is associated with a butterfly fragment comminution. Atypical femur fractures are the result of low energy mechanisms in the elderly. Its radiographic features are associated with cortical thickening and a medial spike. The major criteria include fractures distal of the lesser trochanter, transverse, or short oblique fractures sustained with no or minimal trauma. Complete fractures were associated with a medial spike and incomplete fractures involved only the lateral cortex.17 Minor features commonly have been described in association with atypical fractures but may or may not be present in individual patients; these include periosteal reaction of the lateral cortex, beaking or flaring, focal thickness of the diaphysis of the femur, prodromal dull or aching pain in the groin, bilaterality, and delayed

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healing with use of bisphosphonates or glucocorticoids. The diagnosis of atypical femoral fractures should specifically exclude fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with local primary or metastatic bone tumors, and periprosthetic fractures.

Park-Wyllie published the first paper in JAMA on atypical femur fractures. This was a case control study done in Canada which followed women on bisphosphonates. They identified 716 patients with subtrochanteric or low energy femur fractures and 3,580 matched controls. They found that women treated with bisphosphonates for more than 5 years were associated with an increased risk of subtrochanteric or femoral shaft fractures. However, the absolute risk of these fractures is low.

The American Society for Bone and Mineral Research (ASBMR) appointed a task force to address key questions related to atypical femur fractures. This multidisciplinary expert group included endocrinologist, epidemiologists, radiologists, biomechanical engineers, and orthopaedic surgeons. Their job was to review carefully the currently available information in order to assess what is actually known and what is not known about atypical femoral fractures and their potential relationship with BP usage.

Since millions of women take BP and we now know that there is increased risk of atypical femur fractures with long-term BP use, what is the incidence of these fractures amongst the population? Black and coworkers looked at several clinical trials and tried to determine the risk-benefit of bisphosphonates and atypical femur fractures. Based on the results of several trials, she found that for every 1,000 patients treated 100 fractures were prevented, and approximately one patient sustained an atypical femur fracture.

She concluded that “The occurrence of fracture of the subtrochanteric or diaphyseal femur was very rare, even among women who had been treated with bisphosphonates for as long as 10 years. There was no significant increase in risk associated with bisphosphonate use, but the study was underpowered for definitive conclusions.” The biggest flaw in her study was that it was a retrospective review that did not evaluate all the radiographs, but rather coded the fractures as typical or atypical based on the chart review.

Zehava Rosenberg evaluated 100 asymptomatic patients who were taking bisphosphonates for a minimum of 3 to 5 years. And found that there was 2% incidence of silent “atypical femur fractures,” which was higher than previously thought in the literature.

Pathogenesis of Atypical Femur fractures
BMDD is a measure of the degree and heterogeneity of mineralization in bone tissue. In the healthy adult population, BMDD of cancellous bone shows only minor variations with age, gender, ethnicity, and skeletal site, indicating that the normal BMDD corresponds to a biologic and mechanical optimum. Therefore, even small deviations from the normal BMDD may have biologic meaning. Donnelly and colleagues used FTIR to evaluate the mineral-to-matrix ratio and showed that the range of mineral distribution at the proximal femur is significantly narrower in women treated with BPs for an average of 8 years. Bosky and colleagues in 2009 showed that the increases in mineral density and decreased fracture risk associated with bisphosphonate treatment may be counterbalanced by a decrease in tissue heterogeneity, which could impair tissue mechanical properties. These consistent data suggest that alendronate treatment, while increasing the bone mass, decreases the tissue heterogeneity.

In DM, high glucose levels cause the accumulation of advanced glycation end products (AGEs) that have been associated with an increased risk of fracture in vitro.
and in vivo studies demonstrate that AGE accumulation increases the brittleness of bone. Tang and associates also demonstrated that in dogs high doses of bisphosphonates have been shown to result in the accumulation of AGEs (advanced glycosylation end products) and a reduction in energy absorption of cortical bone. Not only is microdamage accumulation with BP treatment a function of reduced repair, but BP-treated bone also is more susceptible to increased crack initiation, perhaps because AGE accumulation causes bone tissue to become more brittle.

Allen and colleagues did a study with 84 geriatric female beagles, who were treated for 1 year with either risedronate or alendronate at doses equivalent to those used to treat postmenopausal osteoporosis. Vertebræ then were removed and loaded cyclically in compression cycles at loads ranging from 100% to 300%. They found microcracks were significantly more likely to initiate but not necessarily to propagate.

Milgrom and coworkers randomized Israeli military recruits to BP or no BP, and consistent with this hypothesis, treatment with BPs during military training did not lower the risk for stress fractures. That data observed in randomized military recruits was consistent with inhibition of remodeling of stress fractures seen in rats. The effects of BPs on stress fracture repair could be exacerbated if BPs are also antiangiogenic. The periosteum of the femoral shaft is thick and highly vascularized. An effective stress fracture healing response requires an increase in periosteal vascularity. Although some observations identify a direct suppression of vasculogenesis by BPs, it can be difficult in bone to distinguish between inhibition of new vessel growth and suppression of osteoclastic activity because both are coupled. Multiple studies have demonstrated the antiangiogenic effect of BPs on fractures.

**Why the Femur?**

Wolf’s law states that bone in a healthy person will adapt to the loads it is placed under. The femur is similar to a cantilever beam for the body. However, without any bone remodeling, this can be a problem. Constant load without remodeling is similar to repeatedly bending a paperclip until it snaps.

**Management of Atypical Femur Fractures**

When thinking about these fractures, it is important to understand the difference as well as the balance between bone density (quantity of bone) versus bone quality (geometry and properties).

The first step in managing these fractures is to take a medical history of osteoporosis. Specific lab tests can also help to determine the state of a patient’s bone turnover. Imaging is straightforward. Tejwani and Peck published a paper that demonstrated that anterior-posterior and lateral radiographs are reliable for distinguishing between complete femoral fractures related to bisphosphonate use and those not related to bisphosphonate use. Focal lateral cortical thickening and transverse fracture are the most dependable signs, showing high odds ratios and the highest accuracy for diagnosing these fractures. More sophisticated imaging, such as bone scintigraphy, magnetic resonance imaging (MRI), or computed tomography (CT), is useful principally for detecting early or subtle pre-fracture features.

When presented with a patient with a complete atypical femur fracture, the standard surgical treatment is to treat with an intramedullary nail (IMN). However, it is just as important to evaluate their contralateral limb for a possible asymptomatic atypical femur fracture. Bilaterality has been reported to be approximately 28%, mostly via case reports.

Upon evaluating the contralateral femur, it is important to obtain radiographs of the entire femur with AP and lateral views. Further assessment can be made with the patient for more expensive studies based on their pain. If you find them to have an incomplete or asymptomatic fracture, then you can prophylactically IMN or treat them NWB with crutches or switch them to teriparatide.

Teriparatide is an intermittent PTH, which by an unknown mechanism works catabolically by building more bone.

Weil and coworkers examined the outcomes of surgically treated atypical femur fractures. They showed a 47% re-operation rate, with the majority undergoing dynamization. However, these investigators biopsied all of the fracture site, which adds an element of further perosteal stripping to the equation, and they did not elaborate on the postoperative medical management of any of these patients.

Egol and associates evaluated 33 patients with 41 complete atypical femur fractures. Average time these patients were treated with BPs was 8.5 years. Ninety-eight percent healed at 1 year, with the average healing time of 7.9 months, which is longer than the typical femur fractures. Sixty-eight percent returned to their baseline functional status. Pain was cited as the main reason for those who did not return to their baseline.

Using the Bradford Hill Criteria, which is criteria used to demonstrate a causal relationship (Table 2), we can summarize that bisphosphonates do not cause atypical femur fractures but are associated with bisphosphonate use.

In summary, these fractures are rare. Despite their association with BPs, the mechanism of pathogenesis is likely multifactorial and not well understood. BPs do not cause atypical femur fractures, and they are still the mainstay of treatment for osteoporosis. Concerns regarding the association of bisphosphonates and atypical femur fractures should not preclude the use of these agents in the treatment of osteoporosis.

**Disclosure Statement**

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership,
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