

Atypical Femoral Fractures and Their Relation to Bisphosphonate Use

Liana Tripto-Shkolnik MD

Osteoporosis Clinic, Endocrinology and Diabetes Unit, Hillel Yaffe Medical Center, Hadera, Israel

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Much attention and concern over the last several years has focused on a possible connection between prolonged bisphosphonate use and femoral shaft fractures occurring as a result of minor trauma, or, sometimes, no trauma at all. Those fractures have received the title “atypical” to distinguish them from the “typical” osteoporotic fractures of the femoral neck. The purpose of this review is to describe the entity and to critically summarize the mounting research data.

Femoral shaft fractures are classified anatomically as such, when the fracture line lies anywhere below the lesser trochanter (sometimes termed “subtrochanteric”) and above the distal metaphysis. Femoral shaft fractures are, of course, not a new entity. Of all femoral fractures 3%–7% involve the shaft, the majority (around 75%) occurring secondary to major trauma such as road accidents, falls from heights, etc. [1].

Bisphosphonates constitute a major class of medications used to treat osteoporosis and have been on the market for more than 12 years. Their fracture-prevention efficacy was proven in well-designed placebo-controlled trials. Treatment with bisphosphonates reduces vertebral and non-vertebral (including hip) fracture rates. The exact percentage of fracture rate reduction varies from one compound to another and between different fracture sites but, overall, was found to be about 50% in study patients compared to untreated trial participants [2]. The first report regarding a possible connection between prolonged bisphosphonate use and unusual, including mid-shaft, fractures resulting from minor trauma was published in 2005 [3]. Odvina et al. [3] described nine patients who presented with atraumatic fractures of the femoral shaft, proximal femur, sacrum, ischium, pubis and ribs. Most of the patients displayed delayed healing accompanied by suppressed bone turnover. All patients were treated with alendronate, and

some received estrogen and glucocorticoids. These three medications are all bone turnover-suppressing agents.

This report was the first in a long line of subsequent reports aiming to prove or disprove a possible connection between bisphosphonate treatment and atypical osteoporosis fractures. Subsequently, atypical fractures were precisely characterized by a series of clinical and radiological criteria [1]. Numerous case reports were also published, as summarized by Giusti and co-authors [4]. Prior to publication of their review (2010), 141 cases of femoral shaft fractures in patients treated with bisphosphonates were identified. The case reports and case reviews were followed by several retrospective, case-controlled, large epidemiologic studies. Some of those looked at atypical fractures as a “case,” and tried to determine whether those patients received bisphosphonates more often than did control patients with “typical fractures” or no fractures at all. Others defined bisphosphonate treatment as a case and examined atypical fracture incidence in treated versus untreated control subjects.

One such controlled mega-trial retrospectively examined medical claims data for 10 years in the United States, showing more frequent bisphosphonate use in patients with shaft and subtrochanteric fractures than those with other hip fractures [5]. However, interpretation of these data is difficult for several reasons: firstly, there was no information on trauma severity. This is a crucial point since most subtrochanteric fractures are associated with major trauma [1]. Second, the data on bisphosphonate exposure were collected only one year prior to the fracture date, despite the suspicion that the risk is elevated with prolonged treatment. Third, since radiological data were unavailable, the fractures were classified as atypical, based on location alone.

Another recent large Canadian study demonstrated an increased risk for subtrochanteric/shaft fractures with long-term (over 5 years) bisphosphonate treatment, though, again, X-ray data were not available [6]. Of note, the incidence of atypical fractures among women treated with bisphosphonates for 5 years was very low – 0.13% during the subsequent year and 0.22% within 2 years [6].

Using a completely different methodology, a small study from a level one trauma hospital in New York performed

Atypical low trauma fractures of the femoral shaft might be associated with long-term bisphosphonate treatment

a case-control retrospective study of 41 patients identified with low trauma subtrochanteric fractures from 2000 to 2007 [7]. Controls with typical supratrochanteric fractures were matched by age, race and body mass index. All X-rays were reviewed, making these cases reliable in terms of expected distinct fracture patterns [1]. It was found that bisphosphonates were used four times as much in atypical than in supratrochanteric fracture patients. Moreover, there was a correlation between prolonged bisphosphonate use and subtrochanteric fracture risk as well as extent of cortical thickening on shaft X-ray. Similar data pointing at a possible association between femoral shaft fractures and bisphosphonate exposure were collected in Singapore [8] and Sweden [9].

The most recent work, published in June 2012, from Switzerland, attempted to overcome the methodological faults of the previous analyses [10]. The researchers analyzed clinical parameters, drug exposure, and radiological characteristics of patients with atypical femoral fractures compared with classical fractures of the subtrochanteric area, and controls who did not sustain a fracture, for the period 1999–2010. All the admission X-rays were reviewed twice, and bisphosphonate use, if noted in the hospital file, was verified by contact with the patient or his or her family physician, as well as the treatment duration. This study found a very strong association between bisphosphonate use and a risk for atypical fracture as well as a significant positive correlation with length of exposure. Of note, bisphosphonate treatment reduced the risk of classical subtrochanteric fractures by 47% in this cohort, in line with the prospective trial data. Overall, the occurrence of atypical fractures was extremely rare: 32 cases per million person years, with a trend to increase in incidence during the years of the survey [10].

On the other hand, several reports did not confirm the association between bisphosphonate use and subtrochanteric fractures. For instance, a large cross-sectional study from Denmark [11] showed similar percentages of bisphosphonate use in patients with both supratrochanteric and subtrochanteric fractures, including shaft fractures. Again, since radiological data were unavailable and drug history was limited to only one year prior to the fracture, drawing conclusions is somewhat difficult. In another arm of the same report, the incidence of new fractures was examined in the retrospective cohort of patients who started alendronate treatment after typical osteoporotic fracture during 1997–2005, and in the matched cohort of post-fracture untreated patients. Surprisingly, alendronate treatment was associated with a similar increased hazard ratio for both hip and subtrochanteric fractures, leading the investigators to the first conclusion that atypical fractures follow the same epidemiological pattern as osteoporotic fractures.

Another conclusion, or at least, assumption, was that the patients in the treated cohort had a higher fracture risk to begin with, and for that reason treatment was recommended [11]. It is important to note that patients with higher compliance for alendronate treatment (examined as medical possession ratio) had a significantly lower risk for fractures, both at the hip and in atypical sites [11].

Post hoc analysis of pivotal randomized controlled trials testing bisphosphonate (alendronate and zoledronic acid) treatment for fracture prevention did not show increased risk of atypical fractures in the treated group [2], though the studies were not powered for that analysis from the beginning. The same is true for the risedronate trials analysis, which did not support a causal relationship or an association between the use of risedronate and low energy subtrochanteric or diaphyseal fractures (American Society of Bone and Mineral Research 2009 Annual Meeting, Abstract MO0353

These and numerous other studies were summarized in a 2010 report from the ASBMR [1]. The task force established major and minor criteria for atypical fracture case identification. The major criteria, all of which should be present to designate a femoral fracture as atypical, are: location in the subtrochanteric region or femoral shaft, transverse or short oblique orientation, minimal or no associated trauma, a medial spike when the fracture is complete, and non-comminuted fracture. In addition to the criteria formulation, the ASBMR report called for the creation of a specific diagnostic and procedural code and continued basic, epidemiological and clinical research.

Recently, a 2013 second version of the ASBMR report was published and included a criteria revision [12]. According to the newer definition, four of five major criteria (as compared to all) should be present. The absence of comminution has changed to “non-comminuted” or minimally comminuted, and the transverse or short oblique orientation criterion was changed to the following: “the fracture line originates at the lateral cortex and is substantially transverse, although it may become oblique as it progresses medially across the femur.” A minor criterion in the 2010 version, “Localized periosteal reaction of the lateral cortex” was transformed into the major criterion “Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (beaking or flaring).” The newer ASBMR position statement further highlights the relationship between atypical fracture and bisphosphonate exposure, with a positive correlation between exposure length and the risk of atypical fracture. The absolute risk reported varies between studies and ranges from 3.2 to

The incidence of atypical fractures is very low, either absolutely or relative to a high incidence of typical osteoporotic fractures, while the efficacy of bisphosphonates in typical fracture prevention is well established

50 cases per 100,000 person-years; longer exposure is associated with higher risk (100 cases per 100,000 person-years).

Another position paper, from the Working Group of the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis and the International Osteoporosis Foundation, concluded that bisphosphonate use may be associated with atypical subtrochanteric fractures, but that the case is unproven and requires further research and clinical data collection to establish exact prevalence and risk factors [13].

The Food and Drug Administration addressed the issue in their extensive review of bisphosphonate safety in September 2011 (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm270958.pdf>). The conclusion, in conjunct with two previous position statements [1,13], was that atypical fractures are very rare. The mounting data suggest a strong association with bisphosphonate use, although causality has not been determined. The FDA report also discussed available evidence supporting long-term bisphosphonate treatment. In this regard the paper calls for consideration of a drug holiday, although optimal treatment duration, drug holiday timing or its length remains uncertain.

From a practical point of view, atypical fracture should be suspected in a patient with femoral shaft fracture that occurred as a result of minimal trauma (e.g., fall from standing height) or no trauma at all. The characteristic radiological appearance

of complete atypical fracture is transverse or a short oblique fracture line, and a rather “clean,” non-fragmented lesion [Figure 1]. Another important clinical presentation is groin or thigh pain accompanied by a distinct radiological pattern of an incomplete lateral cortex fracture [Figure 2] and localized Technetium uptake on bone scintigraphy [Figure 3]. Since a high rate of contralateral involvement was observed, at least in one study [10], some experts recommend routine radiological evaluation of the unaffected femur in patients with atypical fractures. The preferred treatment of the complete fracture is surgical fixation. The recommended treatment for incomplete fracture is limitation of weight bearing, and, if no clinical and radiographic improvement is evident after 2 to 3 months, prophylactic nail fixation should be considered. As yet there are no established guidelines for medical treatment. If the patient was treated with bisphosphonates prior to fracture, it seems prudent to discontinue the medication. The anabolic option makes

pathophysiological sense; moreover, several reports have indicated a possible efficacy of bone-forming agents in those patients [14].

In summary, do bisphosphonates cause atypical fractures? Conflicting evidence was presented here, yet both the reports that support the connection

and those that dispute it have numerous methodological faults, which makes drawing conclusions somewhat difficult. All the available evidence does point to the fact that atypical fractures are very rare. On the other hand, osteoporotic fractures are common and cause significant morbidity, functional deterioration and even mortality. Bisphosphonates are well-established medications for preventing fractures and their efficacy has been proven in properly conducted prospective trials.

The decision to start a bisphosphonate treatment should be based on comprehensive fracture risk assessment. In higher risk patients, benefits clearly outweigh the possible harm

FDA = Food and Drug Administration



Figure 1. Complete atypical fracture



Figure 2. Incomplete atypical fracture, involving lateral cortex



Figure 3. Localized lateral cortex uptake

The decision to recommend drug treatment (bisphosphonate or non-bisphosphonate) to osteoporotic patients should be based on clinical parameters determining the individual's fracture risk: age, propensity to fall, prior fractures, family history of fractures, medical history, smoking status, body mass index, and finally, bone mineral density. The optimal treatment duration remains a matter for extensive discussion, with little hard evidence to rely on, but the experts' opinions so far suggest reevaluating fracture risk during the course of treatment, thus reducing drug exposure for those in lower risk groups [15].

The crucial point is to offer those medications to patients with a high risk of fractures, for whom the expected well-established benefit from treatment would by far exceed the possible harm.

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Address for correspondence:

Dr. L. Tripto-Shkolnik

P.O. Box 79, Hod Hasharon 45100, Israel

Phone: (972-4) 630-4748

Fax: (972-4) 630-4289

email: lianatrish@gmail.com

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Capsule

CD36 coordinates NLRP3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation

Particulate ligands, including cholesterol crystals and amyloid fibrils, induce production of interleukin 1 β (IL-1 β) dependent on the cytoplasmic sensor NLRP3 in atherosclerosis, Alzheimer's disease and diabetes. Soluble endogenous ligands, including oxidized low density lipoprotein (LDL), amyloid- β and amylin peptides, accumulate in such diseases. Sheedy and team identified an endocytic pathway mediated by the pattern-recognition receptor CD36 that coordinated the intracellular conversion of those soluble ligands into crystals or fibrils, which resulted in lysosomal disruption and activation of the NLRP3

inflammasome. Consequently, macrophages that lacked CD36 failed to elicit IL-1 β production in response to those ligands, and targeting CD36 in atherosclerotic mice resulted in lower serum concentrations of IL-1 β and accumulation of cholesterol crystals in plaques. Collectively, these findings highlight the importance of CD36 in the accrual and nucleation of NLRP3 ligands from within the macrophage and position CD36 as a central regulator of inflammasome activation in sterile inflammation.

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Eitan Israeli

"People rarely win wars; governments rarely lose them"

Arundhati Roy (born 1961), Indian author and political activist best known for her prize-winning novel *The God of Small Things* and for her involvement in environmental and human rights causes