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Review Article

Bisphosphonate induced atypical fractures- The mystery revealed

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Abstract: The incidence of atypical fractures associated with prolonged bisphosphonate therapy has increased because of widespread use for treatment of osteoporosis. They can occur following a minimal or no trauma andpresents as thigh or groin pain. Because of the atypical presentation of these fractures, they may go unnoticed for weeks to months before presenting with a completed femoral fracture. So it's important to keep the overall balance of risks and benefits of bisphosphonate therapy. For some people, the benefits of the bisphosphonate therapies far outweigh the risks involved. The purpose of this article is to highlight the clinico-radiological features leading to early detection and management of such atypical fractures.

Keywords: Bisphosphonates, atypical fractures, teriparatide.

INTRODUCTION

Fracture due to osteoporosis is very common in women above 50 years. Keystone in thetreatment of osteoporosis isbisphosphonate therapy. Bisphosphonatesthat are commonly used are alendronate sodium, risedronate, zoledronate, andibandronate among which, most commonly used and thefirst one to be approved by FDA bisphosphonate is Alendronate sodium [1].Bisphosphonate therapy is very useful in treating osteoporosis in postmenopausal women by increasing bone mineral density thereby reducing theincidence of osteoporotic fractures in hip & spine[2].However, by means of over-suppression of bone turnover, bisphosphonates impair biomechanical properties of bone[3]. When chronically used, bisphosphonates are paradoxically associated with low-energy femoral fractures, also called "atypical femoral fractures". This association has been recently recognized and reported in various studies in the radiology and orthopaedics journals [4,5].

DISCUSSION

Bisphosphonates are normally excreted by kidneys. The residual amount attaches to osteoid tissue and remains attached for years (average half-life ~10 years).Although bisphosphonates are excreted by the kidneys, the amountremaining in the body may attach to the osteoid tissuefor decades[6]. Osteoclasts that resorb bisphosphonatescontaining boneundergo apoptosis as a result of inhibition of farnesyl diphosphatesynthase, an enzyme in the mevalonate pathway that isimportant in the maintenance of the cytoskeleton and for cell survival [7]. The drug residues remaining on thesurface of bones can inhibit future generations' ofosteoclasts. The affinity for attachment to bone surface & half-time in reducing order is for zoledronate, alendronate, ibandronate and risedronate [8]. By suppressing osteoclasts, thereby inhibiting bone turnover, osteoclasts increase bone mineral density, consequently reducing therisk of osteoporotic fractures in thehip as well as thespine.Even after the treatment is over, bisphosphonates may cause inhibition of bone turnover &formationsince theskeletal half-life of bisphosphonates is quite long (average ~10 years)[9]. Bisphosphonatesenter osteoclasts by accumulating in the hydroxyapatite mineral phase of bone and reduce resorption by inhibitingfarnesyl diphosphate synthase, an enzyme in the mevalonate pathway that plays avital role in the maintenance of the cytoskeleton and for cell survival. This, in turn, interfereswith attachment of osteoclasts to thebone surface, inhibiting resorption and finally causes osteoclast apoptosis [10,11]. During remodelingof bone, bone formation by osteoblasts is induced by osteoclasts, hence, reduced resorption lead to reduced bone formation thus poorly affecting bone strength [12].

Correlation between bisphosphonate therapy and atypical fractures has been under debate with two large studies giving different results. A large cohort study from the National Swedish Patient Registry showed that the relative risk of atypical fracture (n=59) with any use of bisphosphonates was 47.3 (95% CI 25.6

to 87.3) while the absolute risk was low, 55 per 100,000 person-years [13]. However, in a recent case-control study in which radiographs were reviewed, atypical fractures (n=10) occurred with equal frequency in bisphosphonate-treated patients and bisphosphonate-naïve patients [14]. In summary, the evidence on the association between bisphosphonate use and atypical fractures is mixed but on balance suggests increased risk of atypical fracture with prolonged bisphosphonate use.

CLINICO-RADIOGRAPHIC FEATURES

The typical presentation is thigh or groin pain in patients who have been on long-term bisphosphonate therapy. History of sharp, prodromal pain localized to mid or upper thigh weeks or months before thefracture is characteristically present. Patients may or may not give ahistory of trivial trauma. Fractures are usually bilateral; hence, the opposite femur should also be imaged.

Atypical fracture attributed to bisphosphonate therapy is defined as a simple transverse or oblique (≤30°) fracture with beaking of the cortex and diffuse cortical thickening of the proximal femoral shaft. Other sites are pubic bones and ischium [15]. Other features are alack of communication, medial spike, anddiaphyseal location. The atypical femoral fracturescan be unilateral or bilateral and occur in the proximalthird of the femur, are usually subtrochanteric(extending from the lesser trochanter to 5 cm distal tothe lesser trochanter) in location. However, occasional occurrence in thesupracondylar region is also seen [16].The most definitive criteria for differentiating atypical proximal femoral fracture due to bisphosphonates from traumatic femoral fractures are focal lateral cortical thickening and a transverse fracture line[1**].**ASBMR (American Society for Bone and Mineral Research) has given major and minor conditions for thediagnosis of atypical femoral fractures. Major condition is fundamental for diagnosis of these fractureswhereas minor condition may/ may not be present [17].

Table 1: Major and minor conditions for diagnosing atypical femoral fractures

Major conditions	Minor conditions
- Absence of any traumatic conditions - Femoral fracture in any diaphyseal location: from below the lesser trochanter to proximal to the supracondylar region - Transverse or short oblique fracture - Non-comminuted fracture - Medial spike incomplete fractures; fractures that involve only the lateral cortical bone in incomplete cases	- Periosteal thickening in the lateral cortical bone - Indicative symptoms - Comorbidities in association with the use of medications that predispose toward fractures - Association with bilateral fracture and/or symptoms

Tc-99m Bone scan reveals increased uptake due to increased osteoblastic activity in proximal femur [18].MRI reveal hypointense fracture line on T1WI, T2WI and STIR sequence with marrow showing diffuse T1 hypointensity & T2 hyperintensity [16].

TREATMENT

NonSurgical Management

Stopping bisphosphonates and providing calcium (1000–1200 mg/day) and vitamin D (30 μg/mL) supplements (to aid new bone formation) before and after bisphosphonate therapy is most important non-surgical treatment.

Surgical Management

Mainstay of surgical treatment remains endochondral fracture repair by intramedullary nailing/ plating depending on thetype of the fracture [2]. In thecase of delayed union, stimulation of fracture healing by removing the distal locking screws along with excessive weight bearing can be beneficial.Treatment can be decided based on bone mineral density assessed by DEXA scan. If T score is less than or equal to −2.5 (osteoporotic patients), treatment with teriparatide (recombinant human parathyroid hormone), subcutaneous injection of 20 μg oncedaily is beneficial. If T score is more than −2.5 (patients with normal bone marrow density), and thepatient does not have any risk factor for vertebral fractures,bisphosphonate therapy can be discontinued and patient needs yearly follow up with DEXA scan. In case T score decreases or another fracture develops, restarting bisphosphonate or teriparatide would help.Patients presenting with cortical thickening only can be treated conservatively or prophylactic nailing may be done [19]. Postoperative administration of Teriparatide improves bone density & aids faster healing in patients previously taking bisphosphonates [20,21].

CONCLUSION

Bisphosphonates, particularly alendronate, have been successfully used as amainstay of treatment of osteoporosis. Despite the effectiveness of bisphosphonates in osteoporosis, there have been cases developing atypical femoral fractures (stress fractures). The absolute risk of developing these atypical fractures is not very high. Hence, bisphosphonate therapy should be judiciously used with regular monitoring (with radiograph/MRI and if required bone scan), particularly after 5 years of therapy. If typical radiological features of lateral cortical thickening with transverse / short oblique lucency& cortical beaking are seen, or prodromal hip pain develops, bisphosphonate therapy should be stopped, calcium & vitamin D

supplementation should be given and prophylactic nailing/ plating should be considered. The role of modification of activities & partial weight bearing is controversial. Postoperative teriparatide therapy should be used for faster healing, particularly in cases of delayed union. However, more controlled trials & studies are required for better understanding of atypical fractures & their management.

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