Bisphosphonate-Related Atypical Femoral Fracture: A Case Series

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Abstract

Aim: The present study reported a case series of atypical femoral fractures related to chronic bisphosphonate use and review the main topics of the disease.

Methods: Our case series were comprised to 8 patients, all female, mean age 74.7 ± 10.8 years (ranging from 57 to 89 years) and 11 femur fractures (3 patients had bilateral fractures) followed between January 2012 and December 2019. All patients were a preceding 6.1 ± 1.1 years history of bisphosphonate use for reported osteoporosis.

Results: Four patients presented with a displaced femoral fracture following minimal or no trauma and reported prodromal symptoms previously to fractures. The other four patients presented with incomplete femoral fracture on radiographs and reported the same symptoms. The average duration of prodromal symptoms was 7.3 ± 4.2 months (range 1 - 12 months). Bisphosphonate therapy was discontinued at the time of admission and administration of calcium and vitamin D were initiated to all patients with incomplete femur fracture and oriented to use crutches and partial weight bearing for three months. Patients complete fractures were conducted to surgery. Intramedullary nailing fixation was the surgical treatment of choice for patients with complete fracture plane (average healing fracture time: 9.1 months). None of the patients with conservative treatment healed in three months and all of them underwent prophylactically Surgery with Nail without distal fixation. For symptomatic incomplete fractures (average healing fracture time: 3.4 months). There were three cases of non-union in patients with complete fracture.

Conclusion: Atypical femoral fractures secondary to chronic use of bisphosphonates represents a spectrum of a disease with a slow evolution that can be insidious in onset and hard to diagnose. Early proactive treatment, with both medical and surgical interventions, may be the key to a good functional outcome.

Keywords: Bisphosphonates; Femoral Fracture; Osteoporosis; Spontaneous Fracture; Stress Fracture

Introduction

Currently bisphosphonates are the single most commonly prescribed medication for the prevention and treatment of osteoporosis [1]. However, these drugs can induce a relative over-suppression of bone turnover and its long-term use has been implicated in increased risks of atypical subtrochanteric and shaft femoral fractures [2,3]. Longer duration of bisphosphonate therapy (e.g. ≥ 3 - 5 years of use) was associated with a higher relative risk for these complications [1,3].

Prodromal symptoms such as dull pain over the lateral aspect of the thigh or groin area often precedes these unusual fractures and are noted around 70% of the patients [4-6]. Furthermore, daily atraumatic activities such as walking, standing, or turning around may be sufficient to fracture.

Signs may be subtle on radiographs, beginning with focal lateral cortical thickening and breaking progressing to development of focal cortical lucency and ultimately a discrete transverse lucent linear fracture line [7]. This finding is sometimes referred to as the "dreaded black line", given the high risk that this incomplete lateral cortical fracture will progress to a complete fracture if left untreated [2].

When clinical suspicion is high enough and simple radiograph appears normal, radionuclide bone scan or magnetic resonance imaging (MRI) examination are mandatory and offer considerably greater sensitivity for early diagnosis and effective treatment [7,8].

Recognizing the disease

Presentation

Some clinicals characteristics of an atypical femoral fracture (AFF) like prodromal pain, bilateral occurrence, cortical thickening and delayed bone fracture healing suggest a specific pathological mechanism when compared with osteoporotic fragility fracture [6].

The incidence of AFFs is higher in woman population aged 50 - 70 years-old [9]. Concomitant exposure to other drugs (e.g. glucocorticoid, estrogen, raloxifene, calcitonin and proton pump inhibitor) in addition to bisphosphonates has been associated with increased risk of fracture [9,10]. Prodromal thigh pain is fairly common occurring around 64 - 71% of patients, with variable duration from days to years before fracture [4-6]. Careful examination of the contralateral femur is recommended because of the high incidence of bilateral lesions, 28 to 55% of patients in some studies [10,11].

The mechanism of fracture is often described by patients as during daily activities and low-energy trauma or is not preceded by obvious trauma [5,6]. Delayed fracture healing is also reported in up to 28% and the duration until complete osseous union has also been shown to be dependent upon the length of bisphosphonate treatment [7,8].

Dell., *et al*. (2012) conducted a cohort study [5] and reported that the age-adjusted incidence rates for an AFF were 1,78/100.000/year (95% CI, 1,5 - 2,0) with exposure from 0,1 to 1,9 years, and increased to 113,1/100.000/year (95% CI, 69,3 - 156,8) with exposure from 8 to 9,9 years. They concluded that incidence of atypical fractures of the femur increases with longer duration of bisphosphonate use. Another large Swedish study of 12.777 women 55 years old or older with femur fracture reported an age-adjusted relative risk of atypical fracture of 47,3 (95% CI, 25,6 - 87,3) in the cohort analysis. A total of 78% of the case patients (atypical fracture) and 10% of the controls (non-atypical fracture) had received bisphosphonates and the risk was independent of coexisting conditions [12].

Imaging

AFF represent a spectrum of a disease entity with a slow evolution and patients can be present at any point along these spectrum [9]. Concerning radiographic appearance, atypical fractures involve a focal thickened cortex or a flare or beak at the lateral cortex that progress to focal cortical lucency and finally a transverse fracture. In contrast, ordinary osteoporotic fractures show a spiral or comminuted pattern and thin cortices [5].

Some others differential diagnoses must be thought during the interpretation of conventional radiographs (Table 1) [2].

Finding	Differential diagnosis
Focal cortical thickening	Normal variant, osteoid osteoma, chronic osteomyelitis/Brodie abscess, stress loading
Periosteal reaction	Infection, surface osteosarcoma, hypertrophic osteoarthropathy
Linear lucency	Normal nutrient vessel channel, osteomalacia
Sclerosis	Chronic osteomyelitis
Bone marrow edema	Transient bone marrow edema syndrome, avascular necrosis, osteomyelitis, tumor

Table 1: Differential diagnosis for stress lesions based on radiographic findings.

MRI may demonstrate early detection bone marrow edema, periosteal reaction, associated with lateral cortical thickening before radiographic findings are apparent [7,13]. Despite this, bone marrow edema is a non-specific finding and must be interpreted in the correct clinical context. It signs can be seen in the setting of neoplasm, infection, fracture, as an incidental finding in asymptomatic adults and

children [2]. If MRI cannot be performed, computed tomography (CT) could detect the cortical fracture or lucency and associated new bone formation. Radionuclide bone scan could detect focal bone and marrow hyperemia but with less specificity than MRI or CT [10].

Diagnosis

American Society of Bone and Mineral Research (ASBMR) task force 2014 defined the criterias for helping to diagnose an atypical femoral fracture [10]. The fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. In addition, at least four of five major features must be presented (Table 2). None of the Minor Features is required but have sometimes been associated with these fractures.

Major features
• The fracture is associated with minimal or no trauma, as in a fall from a standing height or less.
• The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur.
• Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.
• The fracture is noncomminuted or minimally comminuted.
• Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring").
Minor features
• Generalized increase in cortical thickness of the femoral diaphysis.
• Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh.
• Bilateral incomplete or complete femoral diaphysis fractures.
• Delayed fracture healing.

Table 2: ASBMR task force 2014 revised case definition of AFF.

The transverse morphology and subtrochanteric/diaphyseal location contrasts with the spiral subtrochanteric or intertrochanteric fractures seen typically in osteoporotic patients [14]. Therefore, fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (eg, Paget's disease, fibrous dysplasia) are excluded of definition criteria.

Treatment

Proactively treatment with clinical measures is advisable and include immediate interruption of bisphosphonates, administration of calcium, vitamin D, daily subcutaneous injection of recombinant human parathyroid hormone and low-intensity pulsed ultrasound [7]. Some authors suggested the association of teriparatide and strontium ranelate treatment with atypical fracture healing, but no definite conclusion can be reached regarding the efficacy of these medications [15].

Conservative therapy with activity modifications and limited weight bearing may be attempted and vigorous activity avoided for: 1) patients with periosteal thickening but no cortical lucency, or 2) patients with incomplete fractures and no pain. Reduced activity should be continued until there is no bone edema detected on MRI or no increased activity detected on bone scan [10].

Intramedullary reamed nailing fixation is the surgical treatment of choice for: 1) patients with frank fracture plane; 2) prophylactically for incomplete fractures (with cortical lucency) accompanied by pain or 3) if there is no symptomatic and radiographic improvement after 2 to 3 months of conservative therapy, because these patients may progress to a complete fracture [8,10]. These patients should also undergo to the same clinical measures as patients treated nonoperatively. Long nails are preferred over short ones because they protect the entire length of the femur and do not leave a site of increased stress at the end of a short device [9].

Materials and Methods

Our case series were comprised to 8 patients, all female, mean age 74.7 ± 10.8 years (ranging from 57 to 89 years) and 11 femur fractures (3 patients had bilateral fractures) followed between January 2012 and December 2019. All patients were recalled specifically for this study to assess the current physical status. The data was also obtained from medical records and radiographs. Summary all cases shown in table 3.

N	Age (years)	Gender (M/F)	Side (L/R)	Drug	Treatment Duration (years)	Prodromal Duration (months)	Location	Fixation Method	Indication	Healing Time (months)	Complication
Case 1	75	F	L	Alendronate	5	4	Subtrochanteric	Cephalomedullary nail (wdf)	Prophylatic	3	None
Case 2(L)	57	F	L	Ibandronate	5	3	Diaphyseal	Cephalomedullary nail (wdf)	Prophylatic	3	None
Case 2(R)	57	F	R	Ibandronate	5	1	Diaphyseal	Cephalomedullary nail (wdf)	Prophylatic	2	None
Case 3	89	F	R	Ibandronate	6	12	Subtrochanteric	Orthogonal Plates	Therapeutic	18	Osteomielits/ Non-union
Case 4(L)	71	F	L	Alendronate	7	10	Diaphyseal	Cephalomedullary nail	Therapeutic	6	None
Case 4(R)	71	F	R	Alendronate	7	9	Diaphyseal	Cephalomedullary nail	Therapeutic	6	None
Case 5	74	F	R	Alendronate	6	7	Subtrochanteric	Cephalomedullary nail	Therapeutic	8	Non-union
Case 6	82	F	L	Zoledronic Acid	8	12	Diaphyseal	Cephalomedullary nail (wdf)	Prophylatic	4	None
Case 7 (L)	81	F	R	Ibandronate	6	3	Diaphyseal	Cephalomedullary nail	Therapeutic	5	None
Case 7 (R)	81	F	L	Ibandronate	6	4	Subtrochanteric	Cephalomedullary nail	Therapeutic	12	Non-union
Case 8	71	F	L	Risedronic acid	5	15	Diaphyseal	Cephalomedullary nail (wdf)	Prophylatic	5	Proximal Fracture

Table 3: Summary of case series. (R): Right; (L): Left; M: Male; F: Female; wdf: Without Distal Fixation.

Results

Four patients presented to the emergency room tertiary hospital with a displaced femoral fracture following minimal or no trauma. One patient (Case 4) had bilateral fracture at the same time. One patient (Case 7) had complete fracture on the right side and incomplete fracture on the left side that became total fracture after 2 months of conservative treatment. All of them reported continuous pain or tenderness on the lateral thigh previously to fractures. Radiographs showed complete subtrochanteric or diaphyseal fractures extend through both cortices with transverse or oblique line and without comminution. These patients underwent to surgery and in 4 fractures the fixation system of choice was a Long Intramedullary Reamed Nail and in only one case the decision was to use orthogonal plates.

The other four patients were evaluated at outpatient clinic referring the same prodromal symptoms. Radiographs showed thickening or incomplete fracture line on the lateral femoral cortex and medial spike (Figure 1).
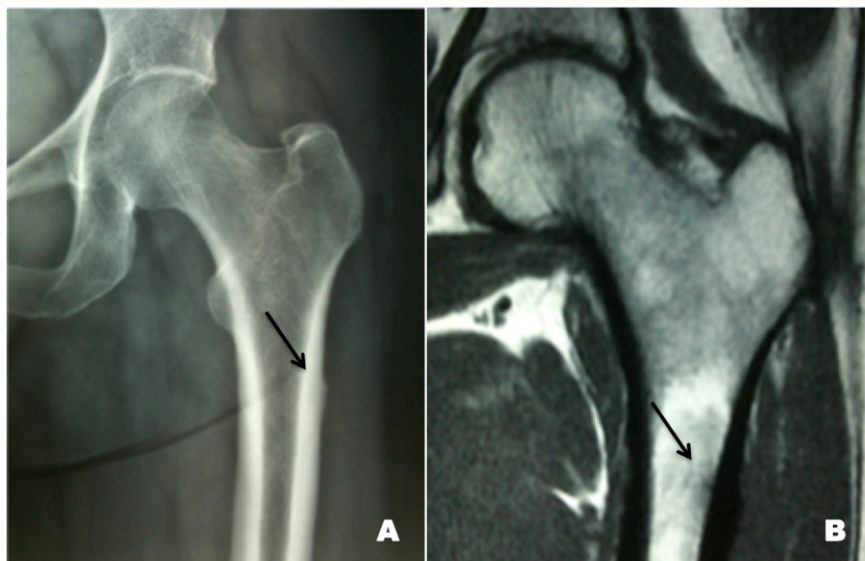
Figure 1: A) Case 2 radiograph shows focal thickened cortex and lateral beak (arrow); B) MRI demonstrates bone marrow edema, lateral cortical thickening and an incomplete fracture line involving the lateral cortex (arrow).

Considering each fracture alone (complete or incomplete), the average duration of prodromal symptoms was 7.3 ± 4.2 months (ranging from 1 to 12 months). Prior to the correct diagnosis, other wrong causes of pain that delayed the treatment had been considered such as fibromyalgia, hip arthritis and trochanteric bursitis.

All patients were a preceding 6.1 ± 1.1 years history of bisphosphonate use for reported osteoporosis without proper follow-up with rheumatologist. After the established stress fracture diagnosis, bisphosphonate therapy was discontinued at the time of admission and administration of calcium and vitamin D were initiated.

Patients diagnosed with incomplete fractures were followed up for up to three months and partial weightbearing with crutches was recommended. None of them healed with conservative treatment and the case 7, had a complete fracture after 2 months and needed to go to emergency surgery again. After 3 months of follow up they were conducted to prophylactic surgery.

Our surgical choice for prophylactic fixation is a Long Cephalomedullary Reamed Nail without distal fixation. Postoperative course was uneventful with total resolution of pain and the average healing time in this group of fracture was 3.0 ± 0.8 months. One patient (Case 8) had proximal femur fracture due to the severe curvature caused by the chronicity of the stress fracture but healed without any consequences (Figure 3). Otherwise, patients diagnosed with complete fractures were treated with Long Cephalomedullary Reamed Nail with distal fixation. Average healing time in this group was 9.5 ± 5.7 months. Radiographic healing was documented as a loss of fracture lucency on the standard anteroposterior and lateral femoral image (Figure 2). Three of six cases of complete femur fractures developed non-union (50%), that needed another procedure: bone graft and dynamization of the Nail, with removal of the static screw.

Intraoperatively one patient with complete fracture had his fixation method modified due to technical difficulties. We could not achieve an acceptable reduction in traction table, conversion to open surgery and fixation with two orthogonal plates (DCP and DCS) were necessaries.
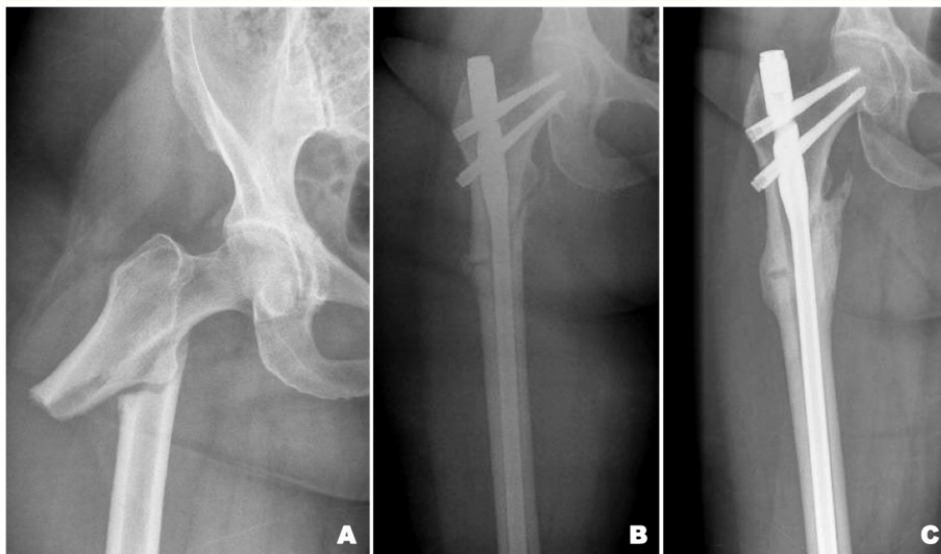
Figure 2: *Case 5 radiographs. A) preoperative; B) first postoperative day of cephalomedullary reamed nail with distal fixation; C) 8th postoperative month with fracture healing after nail dynamization and bone graft.*
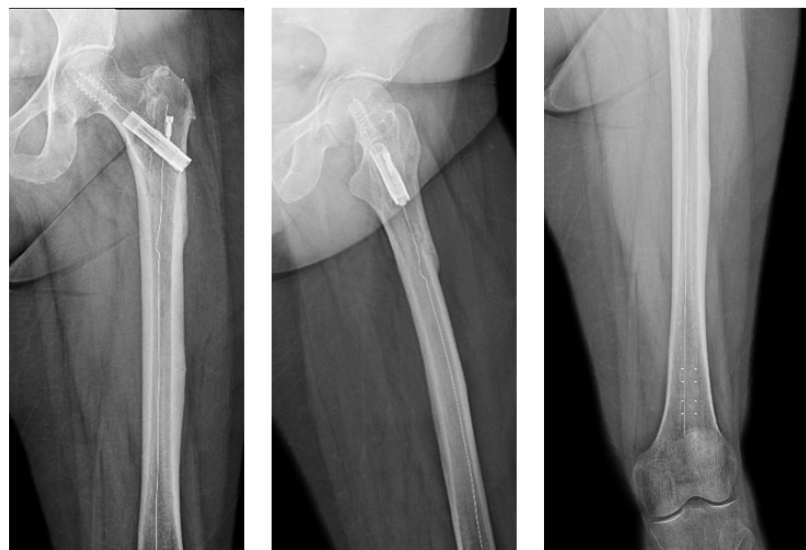

Figure 3: *Case 8, Carbon Nail was used for Prophylatic fixation. Proximal fracture was observed but healed without any consequences. No distal fixation was needed.*

During surgical procedures, medullary bone were collected and sent for anatomopathological evaluation and in 5 of 11 cases (45%) revealed multiple sites of osteonecrosis (Figure 4).
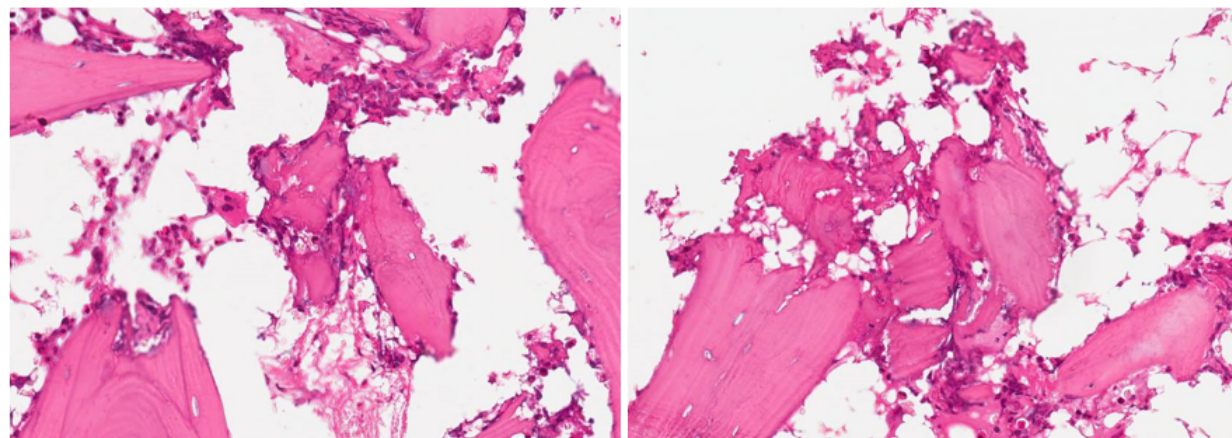

Figure 4A and 4B: *Case 4 left and right sides showing osteonecrosis.*

We had three cases of non-union in patients with complete fracture. Two of them were treated after 6 months with nail dynamization and bone graft. The third case (Case 3) developed non-union and osteomyelitis by a multi resistant *Escherichia coli*, the same isolated in the urine that had been collected on the admission day. She was treated with surgical debridement and antibiotic therapy for 20 months. Healing occurred after 18 months of surgery, which was confirmed by computed tomography scans. However, because of the persistent subclinical infectious condition, the plates were removed after 2 years. On 43rd postoperative day the patient had a refracture at the same location and was treated with a cephalomedullary nail with distal fixation and satisfactory outcome.

In all cases the option to use the cephalic screw was made in order to protect the femoral neck. In any case short implant was used because of the risk of associated shaft fracture. For Incomplete fractures we used and recommend as prevention of fat embolism a reamer with suction system, as the bone is almost intact and the pressure during reaming can be very high. All patients began hip and knee motion exercises, and partial weight bearing as tolerated was allowed immediately after surgery with a walker.

Discussion

Bisphosphonates are current FDA-approved pharmacologic options (alendronate, ibandronate, risedronate, and zoledronic acid) for the prevention and/or treatment of postmenopausal osteoporosis, osteoporosis in men and osteoporosis due to long-term glucocorticoid therapy [16].

Although these drugs are potent anti-resorptive agents and were proven to be effective to ameliorate the effects of senescent osteoporotic changes [1,7], its excessive suppression of normal and pathologic bone remodeling has been a concern [8]. Their primary course of action is to inhibit bone resorption by the induction of osteoclast apoptosis and increased osseous density. However, the loss of general bone turnover result in a cancellous bone inherently more brittle and less resilient to microtrauma [7].

It is increasingly evident in the literature the side effects of chronic use of bisphosphonates. Odvina., *et al.* (2005) first report a case series of nine women with atypical fractures possibly related to long-term bisphosphonate treatment [17]. In a recent study of over half-a-million senescent females, Wang., *et al.* (2014) showed that higher exposure to bisphosphonates was associated with increased risk of subtrochanteric and femoral shaft fractures, in contrast to significant reductions of intertrochanteric and femoral neck fractures [3]. A meta-analysis conducted by Gedmintas., *et al.* (2013) estimates an adjusted risk ratio for AFF associated with bisphosphonates using data from the five case-control and six cohort studies as 1.70 (95% CI, 1.22 - 2.37) [18].

In addition to atypical fractures, short and long-term side effects has been described. Some short-term side effects include gastrointestinal symptoms, delayed esophageal emptying, hypocalcemia iritis and renal toxicity. Long-term side effects include musculoskeletal pain, atrial fibrillation, esophageal cancer, osteonecrosis of the jaw [16].

After the initial 3 - 5 years treatment period, a comprehensive risk assessment should be performed to decide about the continue or discontinue bisphosphonate use. This decision should be based on clinical history, height measurement, bone mineral density testing and vertebral imaging [1]. Duration decision should be individualized and reviewed annually. The higher the duration and adherence of therapy, the higher the risk of atypical femoral fracture [3,5,8]. The good news is that a break in bisphosphonate therapy may "reset the clock" on AFF [16]. Schilcher., *et al.* (2012) reported a 70% reduction in risk for every year since the last use (multivariable adjusted odds ratio, 0.28; 95% CI, 0.21 to 0.38) [12].

In 2014 the American Society of Bone and Mineral Research (ASBMR) task force defined the criterias for the diagnosis and better standardize the reporting of atypical femoral fractures [10]. Five major features were described: minimal or no trauma event; transverse fracture line originates at lateral cortex; medial spike in complete fractures; minimal or no comminution of fracture and focal thickening at the fracture site.

Although bisphosphonates prevent typical osteoporotic fractures, these drugs are related to occurrence of atypical osteoporotic fractures. Increased caution may be indicated in long-term users where the benefit of prevention is less clear. Nowadays there is a consensus that a drug discontinuation ("drug holiday" for 1-2 years) after 3 - 5 years of use of bisphosphonate is advisable in asymptomatic patients who have demonstrated an improved T score ≥−2.0 and no antecedent osteoporotic insufficiency fractures [5,14,18,19].

Instead of all this preoccupation, with a correct indication, the benefits of fracture prevention with bisphosphonate use still greatly outweigh the risk of atypical femoral fracture and cannot be forgotten [12].

Conclusion

Long Cephalomedullary Nail is the best option for complete atypical femoral fracture. Prophylactic fixation with Long Cephalomedullary Nail should be done as soon as possible to avoid a complete fracture. In our group of patient's distal fixation for incomplete fractures was demonstrated that is not necessary. Osteonecrosis can be a possible explanation of these problems.

Conflict of Interest

None.

Informed Consent

All involved persons gave their informed consent prior to study inclusion.

Author's Contribution

Maurício: Surgical Procedures; Acquisition of Data; Preparation of Manuscript.

Alexandre: Review of Manuscript; Surgical Procedures.

Jader: Acquisition of Data; Review of Literature; Preparation of Manuscript.

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