

Are the Atypical Femoral Fractures a problem in order to Osteoporosis Treatment?: Its Management and Consequences

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Received date: Oct 15, 2015; Accepted date: Nov 17, 2015; Published date: Nov 19, 2015

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Abstract

Introduction: Bisphosphonates (BPs) evolved as the mainstay for the treatment of osteoporosis, reducing the incidence of fractures. Recently several publications described the occurrence of low-energy sub-trochanteric and femoral shaft fractures associated with long-term BPs use; those have been defined as atypical femoral fractures (AFF). The aim of this study was to value the influence of BPs on the shaft and sub-trochanteric fractures and to describe the outcome of surgically treated femur fractures associated with prolonged BPs use.

Material and Methods: Between 2010 and 2014, a total of 129 patients 50 years and older were hospitalized with a sub-trochanteric or femoral shaft fracture at a single university medical centre. Admission x-ray and medical and treatment records were examined, and patients were classified as having atypical or classic femoral fractures. X-ray and clinical controls were assessed to describe the healing-fracture process. Chi-square test was used to assess the association of bisphosphonate use and atypical femoral fracture.

Results: Fourteen patients with AFF (10, 8%) and 115 patients with typical fractures (89, 1%) were identified. All patients with AFF had been treated with BPs (100%), compared with 7 (6%) in the typical fractures group (Chi-square statistic was 80.76. This result is significant at $p < 0.05$). The mean BPs use was 56, 7 months in the AFF while in the typical fractures was 63,6 months ($p > 0.05$). A contralateral fracture occurred in 2 of atypical cases. The mean time of bone consolidation was 13,2 months in AFF and 11,6 months in typical fractures ($p > 0.05$). The follow-up was 38, 4 months in AFF and 40,6 in typical fractures ($p > 0.05$). No reoperations were identified in the patients with AFF, while 13 reoperations were observed in the patients with typical fractures (2 dynamizations, 9 exchanges nail and 2 plates) ($p < 0.05$).

Conclusions: The BPs use increased AFF respect to typical fractures in our population. The patients with an AFF must be stopped and an anabolic agent should be employed. These patients should also have daily calcium and vitamin-D supplementation. No more reoperations were observed in patients with AFF who were treated with an intramedullary nail compared with patients who suffered typical fractures.

Keywords: Bisphosphonates; Femur Fractures; Osteoporosis; Fragility Fractures.

Introduction

Bisphosphonates (BPs) reduces bone loss and prevent fractures in postmenopausal women with osteoporosis, in men with osteoporosis [1,2], and in patients receiving glucocorticoid (GC) therapy. In the past decade, however, osteonecrosis of the jaw (ONJ) [3] and atypical femoral fractures (AFF) [4,5] have emerged as potential complications of BPs and, more recently, denosumab therapy. In contrast to ONJ, which came to attention in patients receiving highdose BPs therapy for malignancy, most though not all patients with AFF were receiving the lower doses of BPs typically used to treat osteoporosis or osteopenia [6].

While the mechanism of this is unknown, studies suggest that BPs may negatively affect bone remodelling and lead to increased micro damage [7,8]. Unlike typical hip fractures found in the femoral neck, trochanteric, and intertrochanteric regions of the femur, AFF occur in the sub-trochanteric and femoral shaft regions. Fractures in the sub-

trochanteric or femoral shaft regions are rare, with some studies estimating 3-50 fractures per 100.000 person-years in certain populations [9]. However, while the incidence of hip fractures is decreasing in the US and Europe, the incidence of sub-trochanteric and femoral shaft fractures is stable or possibly increasing [10]. The reports are controversial and the detailed mechanism of this phenomenon is unknown. Recently, two meta-analysis have been published and its conclusion is that there is an increased risk of sub-trochanteric, femoral shaft, and atypical femoral fractures among BPs users [11,12].

The guideline used as model was carried out by American Society for Bone and Mineral Research (ASBMR), which organized a multidisciplinary task force in 2009 and published a position paper in 2010 about the AFF, which was defined as a traumatic or low-trauma fractures located in the sub-trochanteric region or the femoral shaft. High-trauma fractures, femoral neck fractures, intertrochanteric fractures with spiral sub-trochanteric extension, pathological fractures associated with primary or metastatic bone tumours, and peri-prosthetic fractures were excluded from the diagnosis of AFF. Other major features of AFF included transverse or short oblique

configuration, non-commented in-complete fractures involving only the lateral cortex, while complete fractures extend through both cortices and might have a medial spike. Minor features comprise localized periosteal reaction or breaking of the lateral cortex, generalized cortical thickening of the femoral shaft, a history of prodromal pain, bilateral fractures and symptoms, and delayed healing in association with certain medication and medical conditions. All major features were needed to define a fracture as “atypical” while minor features might not be present in some cases [4]. Recently, ASBMR published an updated version of previous 2013 report that included revised criteria for AFF. According to the new definition, four of the five major criteria (versus all) should be present to define an AFF. The absence of comminution was changed to “non-comminuted” or minimally commented, and the transverse or short oblique orientation criterion was changed to “the fracture lines originate 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 incorporated as a major criterion: “localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (breaking or flaring)”. Reasons for changes were a positive correlation between BPs use and signs of fatigue fractures, including transverse fracture lines on the lateral cortex, periosteal reactions, and a medial spike. “Short oblique fracture line” was also deleted from the new criteria because the definition of short oblique may differ from one physician to another and most orthopaedic surgeons consider a fracture short oblique when the angle between the transverse axis and the fracture is less than 30°. When “short oblique” is used to define an angle between 30 and 60°, the positive association between BPs use and AFF falls dramatically (13). Compared with the 2010 position, the 2013 ASBMR position statement further clarified the relationship between AFF and BPs exposure, reporting a positive correlation between exposure time and the risk of atypical fractures [4,13].

Most orthopaedic surgeons recommend an intramedullary full-length reconstruction nail as the preferred method of treatment [14,15]. The outcome of surgical treatment in patients with bisphosphonate-related AFF is discussed because of theoretically BPs influence on the healing-fracture process [14].

The aim of this study was to value the influence of BPs on the shaft and sub-trochanteric fractures in our population and at the same time to describe the outcome of surgically treated femur fractures associated in these patients and to add relevant clinical information about these uncommon fractures.

Material and Methods

This cases study included all patients 50 years of age and older who were admitted to our Hospital with a fracture of the sub-trochanteric or femoral shaft area between January 1, 2010 and December 31, 2014. We selected 2 major fracture subtypes as defined by the International Statistical Classification of Diseases, 10th Revision, including femoral sub-trochanteric fractures (S72.2) and femoral shaft fractures (S72.3).

We excluded patients with fractures resulting from high-energy trauma fractures caused by tumours (either metastatic or primary) or documented Paget disease of bone; fractures involving an implant within the fracture line; and intraoperative femoral shaft fractures. Patients with conditions that might be associated with altered bone integrity, such as osteomalacia, osteopetrosis, hypercalcemia, hyperparathyroidism, celiac disease, and renal osteodystrophy, also were not included.

All patients (N=129) presenting with an initial sub-trochanteric (S72.2) or femoral shaft (S72.3) fracture during the study period were identified as having either atypical fractures or classic fractures based on admission standard radiographs of the entire femur. Atypical fractures were characterized according to the criteria listed in the American Society of Bone and Mineral Research task force report of 2013 [13].

The occurrence of previous or current bisphosphonate treatment (alendronate, risedronate, pamidronate, ibandronate, etidronate, or zoledronic acid) was assessed by detailed examination of the medication list included in the computerized hospital medical records. This assessment was done for each patient who presented with a sub-trochanteric fracture (S72.2) and femoral shaft fracture (S72.3). Radiographic healing was defined as callus bridging of three of four cortices on antero posterior (AP) and lateral radiographs [16] corresponding to RUST score of at least 8 to 9 [17], as well as painless weight bearing on the affected extremity.

Statistical Analysis

Statistical analysis consisted of descriptive statistics using means, medians, and standard deviations for continuous variables and frequencies and percentages for discrete variables. All demographic and clinical variables were assessed statistically for an association with the occurrence of AFF. Categorical data were analysed using Mantel-Haenszel chi-squares for matched analysis and Pearson's chi-square or Fisher's exact test as appropriate for unmatched analysis. Independent samples t tests and one-way analysis of variance were used to compare continuous variables. Mann-Whitney and Kruskal-Wallis were used for non-parametric data where appropriate. Correlations were calculated using the Spearman rank correlation. For those subjects who had an AFF, the time on bisphosphonate to fracture was assessed and alpha was set to 0.05 for all analyses. Relative risk estimates are represented as odds ratios (OR), the probability of an event in the AFF versus the Typical Fractures, with 95% confidence intervals (CI).

Results

One hundred twenty-nine fractures were identified in 126 patients. Fourteen fractures were characterized according to the criteria listed in the American Society of Bone and Mineral Research task force report of 2013 in 12 patients (2 patients had bilateral fractures). Comparative results are showed in [Table 1], and AFF characteristics are showed in the [Table 2].

	Number	Years (range)	BFs	Reoperations	Follow-up (range)	Consolidation (range)
Typical Fractures	115 (89,1%) of 129	78 (62-95)	7 (6%), mean 63,6 months	8 (6,9%)	40,6 (12-58)	11,6 (8-18)

Atypical Fractures	14 (10,8%) of 129	66 (60-74)	14 (100%), mean 56,7 months	0 (0%)	38,4 (10-56)	13,2 (8-20)
P value AFF vs Typical Fractures	0,041	0,025	0,002	0,032	0,87	0,91

Table 1: Comparative statistics between AFF and typical fractures.

Statistic differences were found in the median age, this was 66 years in AFF and 78 years in typical fractures ($P < 0.05$). The mean BPs use was 56, 7 months in the AFF while in the typical fractures was 63, 6 months ($p > 0.05$). All patients with an AFF used BFs, whereas 7

patients with typical fractures used BFs, we found an association between the use of BFs and the risk to suffer an AFF (The Chi-square statistic was 80.76. This result is significant at $p < 0.05$).

	Location	Use before BFs (months)	BF type	Surgery	Consolidation (months)	Reinterventions	Follow-up
Case 1	Shaft	72	Alendronate	Intramedullary nail	14	No	52
Case 2	Shaft	64	Alendronate	Intramedullary nail	20	No	40
Case 3	Sub.	54	Alendronate	Intramedullary nail	18	No	50
Case 4	Shaft	54	Alendronate	Intramedullary nail	14	No	36
(Figure 4)							
Case 5	Sub.	78	Risedronate	Intramedullary nail	10	No	40
Case 6	Shaft	48	Alendronate	Intramedullary nail	16	No	26
Case 7	Sub.	56	Alendronate	Intramedullary nail	8	No	38
Case 8	Shaft	58	Risedronate	Intramedullary nail	14	No	46
Case 9	Shaft	44	Alendronate	Intramedullary nail	10	No	38
(Figure 3)							
Case 10	Sub.	76	Zoledronic acid	Intramedullary nail	18	No	56
Case 11	Shaft	46	Alendronate	Intramedullary nail	8	No	48
Case 12	Shaft	46	Alendronate	Intramedullary nail	16	No	26
Case 13	Sub	56	Alendronate	Intramedullary nail	8	No	10
(Figure 1 and 2)							
Case 14	Shaft	42	Alendronate	Intramedullary nail	12	No	32

Table 2: AFF characteristics.

Statistic differences were found in the median age, this was 66 years in AFF and 78 years in typical fractures ($P < 0.05$). The mean BPs use was 56, 7 months in the AFF while in the typical fractures was 63, 6 months ($p > 0.05$). All patients with an AFF used BFs, whereas 7 patients with typical fractures used BFs, we found an association between the use of BFs and the risk to suffer an AFF (The Chi-square statistic was 80.76. This result is significant at $p < 0.05$). The mean time of bone consolidation was 13,2 months in AFF and 11,6 months in typical fractures ($p > 0.05$). The follow-up was 38, 4 months in AFF and 40, 6 in typical fractures ($p > 0.05$). No reoperations were identified in the patients with AFF, while 13 reoperations were observed in the patients with typical fractures (2 dynamizations, 9 exchanges nail and 2 plates) ($p < 0.05$). Intramedullary nail was used as treatment by all

fractures as first treatment (AFF and typical fractures). Alendronate was the BF more used in patients with AFF (8 patients), Risedronate was used for 2 patients and Zoledronic Acid was used for 1 patient.

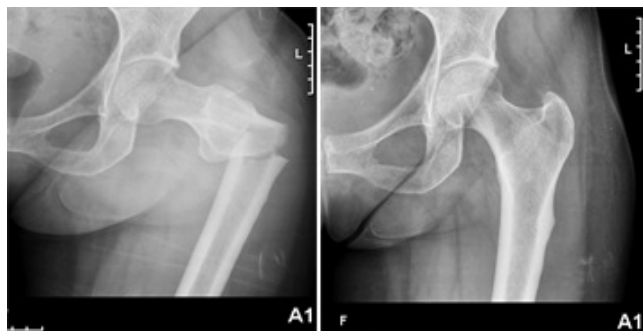


Figure 1 and 2: (Case n° 13) Figure 1, this image represents the x-ray 3 months before to suffer the fracture, which we can see the cortical thickening that was suggestive of fatigue fracture. Figure 2 show the sub-trochanteric fracture with a short oblique line, where the angle between the transverse axis and the fracture is less than 30°.



Figure 3: (Case n° 9), this image shows a shaft femoral fracture with a medial spike.



Figure 4: (Case n° 4), this image shows a shaft femoral fracture with the medial spike.

Discussion

A prodromal thigh pain appears before to develop an AFF. In our series all patients described this pain, but only 8 patients consult it. So, it is necessary to educate physicians and patients about this symptom. Physicians should ask patients on BP and other potent anti-resorptive agents about thigh or groin pain [13,15]. In addition, cortical thickening is suggestive of fatigue fractures. Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) is necessary to further investigate the nature of the lesion. MRI detects a cortical fracture line and associated bone marrow edema or hyperaemia, which indicates a fatigue fracture and/or associated new bone formation. If cortical lucency is detected from CT or MRI, then the lesion should likely be considered an incomplete AFF. In our series only 3 patients had x-ray made, which it was seen this cortical reaction. If a stress reaction is detected, BPs should be discontinued. Adequate calcium and vitamin D supplementation is recommended. If pain accompanies the lesion, intramedullary nailing is usually necessary. If there is minimal pain, the patient can be observed with limited weight-bearing through use of crutches or a walker for 2-3 months. If symptomatic and radiographic improvement is not achieved after the period, prophylactic nailing should be considered. If periosteal thickening is observed without associated radiolucency, limited weight-bearing may be continued for another 3 months and reassessed [13,15]. Our 3 patients with cortical reaction observed stayed with weight-bearing, but the diagnosis of AFF was not made, so the fractures appeared at 5, 7 and 8 months since the pain was detected by the patient, without remove the BPs use.

Teriparatide has been used increasingly for AFFs because of its bone-forming properties. Although there has not been a randomized, placebo-controlled trial to prove its efficacy, teriparatide can be considered for these fractures that do not appear to heal with conservative treatment. Teriparatide could also be used when there is little evidence of healing by 4-6 weeks after surgical intervention [15].

Although there are not randomized controlled trials comparing a plate-and-screw construct and intramedullary nail fixation for the treatment of atypical femoral fractures, most orthopaedic surgeons recommend an intramedullary full-length reconstruction nail as the preferred method of treatment [14]. A fracture treated by intramedullary nailing heals by endochondral repair, whereas a plate-and-screw construct generally precludes the endochondral repair process and is not recommended for these fractures [15]. The outcome of surgical treatment in patients with bisphosphonate-related atypical femoral fractures is poor according to Weil et al [14], who showed seven (44%) of sixteen fractures treated with intramedullary nail fixation required secondary operative procedures. Although some studies suggested a potential negative effect of bisphosphonates on the fracture-healing process, current evidence shows conflicting results. Visekruna et al. (18) reported on three patients with atypical sub-trochanteric fractures, one of which had no radiographic evidence of union at twenty-two months. Conversely, Ha et al. [19] reported that ten atypical femoral fractures all healed, with osseous union after internal fixation during the follow-up period of twelve to sixty months. These differing results may be due to differences in preoperative status and in the medication type or dose used in these patients. Our results differing with Weil et al and Visekruna et al [14,18], given that we have had 14 patients treated with intramedullary nail and no second operative procedures were necessary, this results are according to Ha et al. Bone consolidation was identified on the x-ray to 13,2 months (between 8 and 20), very similar to patients with typical fractures [11,6]. This fact call doubts about the explanation offered by Weil

about the potential negative of BFs on the fracture-healing process. In addition, our patients with an AFF were more significantly younger than the patients with a typical fracture (66 years AFF and 78 years typical fractures). This result is completely logical because of typical fractures are associated to fragility bone of old age, so the patients younger could suffer AFF more easily than typical fractures.

Unnantamuna et al. [15] recommend careful surveillance of patients with AFF because 28% to 44.2% of patients with AFF have bilateral involvement. Radiographs of the contralateral femur must be evaluated for evidence of a stress fracture. In our series 14% suffered a bilateral fracture. One of our patients was 16 months without BPs treatment. She noted pain in her contralateral thigh 8 months after the first fracture, but no cortical reaction was detected and finally she suffered the fracture. Other patient was 24 months without BP treatment. The bone consolidation was tested 10 months after the fracture. She complained of thigh pain 20 months after the first fracture, but, unfortunately, she suffered the fracture without contralateral diagnosis.

It is recommended that osteoporosis treatment with BPs be stopped after a period of five years to provide patients a so-called “drug holiday.” The duration of BPs treatment and the length of the drug holiday are based on fracture risk and the pharmacokinetics of the BPs used [20]. Park-Wyllie et al. [21] performed a nested case control study to explore the association between BPs use and femoral fractures, and they reported that BP treatment of more than five years was associated with an increased risk of atypical sub-trochanteric or femoral shaft fractures. We have confirmed these results in our patients. Therefore, it may be appropriate to consider a drug holiday in patients with a cumulative duration of BPs treatment of more than five years according to Unnantamuna et al [15]. However, our results fall this time, because 10 of 14 patients suffered fractures with less of 5 years of BPs treatment (56,7 months), so this time may be reconsidered in further investigations and prospective studies on different populations. For patients at low risk of fracture, BPs can be discontinued and the patients placed on a drug holiday. Patients should nevertheless take daily calcium and vitamin-D supplements. For those at high risk of fracture, it may be beneficial to continue BPs treatment beyond five years. Alternatively, other medications such as denosumab or teriparatide may be provided during the holiday from BPs. For patients at moderate risk of fracture, the management plan can be further divided on the basis of the bone turnover state (low and high-turnover states). Patients who are at moderate risk of fracture and in a low turnover state can be managed in a fashion that is similar to those at low risk of fracture. However, patients who are at moderate risk but in a high-turnover state should be managed as if they have high risk of fracture. The drug holiday should be continued until there is substantial loss of bone mineral density, marked increase in bone turnover markers, or the occurrence of a new fracture [20].

A weakness of this study was the absence of assessment of baseline bone density from DEXA, which provides us information about individual bone characteristics. However, only 3 patients of the AFF group had made this test, because, unfortunately, in our region have not established as screening. So, this important information have not could help us to explain the peculiarities of the bone of the AFF. Assessment of Baseline bone density.

In conclusion, the relationship between BPs use and atypical femoral fractures has not yet been established, but if a patient sustains an AFF, BPs must be stopped and an anabolic agent should be employed. These patients should also have daily calcium and vitamin-D supplementation. As fractures treated by intramedullary nailing heal

by endochondral repair, such nailing is a preferred method of fixation for atypical femoral fractures. No more reoperations are waited in patients with AFF, although more studies are necessary about this aim. AFF are relatively rare events, and the balance between patient efficacy and safety still favours BPs therapy for the treatment of osteoporosis. BPs appear to have lingering efficacy against fractures more studies are necessary to guide the clinician in regard to optimal approach of BPs administration in osteoporotic patients to minimize these rare, but serious complications even after the treatment is discontinued, so a drug holiday should be considered for most patients who take BPs for five years or more, according to actual evidence, but more studies are necessary about this question. Because many questions regarding atypical femoral fractures are unanswered, future studies should focus on bone properties of the femoral cortices as well as the healing-fracture process and the influence of BFs in this event.

Disclosure

This work was performed in the Complexo Hospitalario Universitario de Ourense.

All patients accepted that we used their information (including photos) to prepare this paper.

Any author of this manuscript receive funding, grants, or in-kind support in support of the research or the preparation of the manuscript. Any author have association or financial involvement (i.e. consultancies/advisory board, stock ownerships/options, equity interest, patents received or pending, royalties/honorary) with any organization or commercial entity having a financial interest in or financial conflict with the subject matter or research presented in the manuscript.

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