

# Atypical femoral fractures: retrospective radiological study of 319 femoral fractures and presentation of clinical cases

V. Bottai · S. Giannotti · G. Dell’osso · G. De Paola ·  
A. Menconi · F. Falossi · G. Raffaetà · G. Guido

Received: 24 July 2013 / Accepted: 2 October 2013 / Published online: 31 October 2013  
© International Osteoporosis Foundation and National Osteoporosis Foundation 2013

## Abstract

**Summary** There is still no clarity on the etiology and epidemiology of atypical femoral fractures. The purpose is to show, after a radiological review, that the incidence of atypical fractures is higher than that reported in the literature when compared to “typical” fractures that occurred in the same anatomical site.

**Introduction** At present, it is difficult to define the true incidence of atypical fractures associated with bisphosphonate. Our purpose is to show that the incidence of atypical fractures is higher than that reported in the literature when compared to “typical” fractures that occurred in the same anatomical site.

**Methods** The authors analyzed 319 femoral fracture RxS of patients over 60 who have had access to the PS of Clinical Orthopaedics and Traumatology II of the University of Pisa from January 2011 to February 2013. The atypical fractures have been investigated from clinical point of view, biohumoral exams, densitometry and contralateral femur X-rays, and in one case using SPECT-Tc.

**Results** The total number of femoral fractures was 319. The medial femur fractures were 60 (46 females and 14 males), and the lateral ones were 316 (237 females and 79 males). Subtrochanteric and diaphyseal fractures were 40 (29 females and 11 males). Among these cases, two atypical fracture cases were related to female patients, one was 79 years old and the other was 77.

**Conclusions** The most recent literature reports that the incidence of atypical fractures is 0.6 %. However, taking into consideration only the fracture locations suitable for the identification of atypical fractures, the percentage rises to 5 %. To

date, there is still no clarity on the exact etiology of fractures even if it seems to be related to a bone mineral component alteration.

**Keywords** Atypical · Bisphosphonate · Femoral fracture · Osteoporosis

## Introduction

The bisphosphonates are drugs widely used to treat osteoporosis, especially in patients treated with corticosteroid [1, 2].

Bisphosphonates have high effectiveness in the treatment of osteoporosis. Numerous large clinical trials have demonstrated their effectiveness in reducing bone turnover, increasing bone mineral density and reducing vertebral and non-vertebral fracture risks in patients with osteoporosis [3, 4].

Contrasting their beneficial effect, since 2005, there have been increasing concerns regarding the potential risk of an unusual type of femur fracture among patients on bisphosphonate therapy [5]. Similar fractures were later described by Lenart and colleagues as “atypical” in that they involved the strongest part of the femur, namely the subtrochanteric and diaphyseal region, and were characterized by features distinctly different from “typical” osteoporotic femur fractures [6].

There are more and more studies that show a possible relationship of bisphosphonates with the occurrence of atypical fractures defined by the Task Force of the American Society for Bone and Mineral Research. They are defined as subtrochanteric or diaphyseal fractures, atraumatic or caused by minor trauma, transverse or oblique, and complete or incomplete departure from the lateral cortex [7].

The epidemiology of these fractures is not easy to define since there is no identification code ICD-9 being evaluated in retrospective studies [8].

V. Bottai · S. Giannotti (✉) · G. Dell’osso · G. De Paola ·  
A. Menconi · F. Falossi · G. Raffaetà · G. Guido  
II Clinica Ortopedica E Traumatologica, Università’ Di Pisa,  
Via Paradisa 2, Pisa, Italy  
e-mail: s.giannotti@med.unipi.it

Until now, the incidence of atypical fractures is estimated to be about 1 % of femoral fractures, with a 0.4 % of this 1 % associated to bisphosphonates [9]. It is estimated that under 65 years, 0.1–0.2 people over 10,000 per year had an atypical fracture without association with bisphosphonates, while in people over 65 years, this incidence increases to 1.6 over 10,000 per year. When considering the patients treated with bisphosphonates, the incidence of atypical fracture is estimated 3–10 over 10,000 patients per year [10].

Subtrochanteric fractures have important effects on mortality and morbidity. A study over 87 patients with subtrochanteric fractures showed a mortality rate of 14 % within 12 months and 25 % within 24 months. Moreover, before 24 months, almost half did not achieve their prefracture ability to walk and to perform other daily activities.

The predominant hypothesis regarding the pathophysiology of atypical femur fractures is that severe suppression of bone turnover leads to the accumulation of bone microdamages and the development of an insufficient resistance to fracture at the point of maximal, weight-bearing stress, namely at the subtrochanteric or diaphyseal femur [11, 12].

The involved factors are many: alterations to the normal pattern of collagen cross-linking, changes to maturity of cross-links formed by enzymatic processes, advanced glycation, end-product accumulation, microdamage accumulation, increased mineralization, reduced heterogeneity of mineralization, variations in rates of bone turnover, reduced vascularity, and antiangiogenic effects.

## Materials and methods

The authors present the results of a review of 319 radiographic fractures of the neck of the femur. First, the authors have selected only the Rxs presenting the typical features of atypical fractures regardless of the anamnesis data. Then an accurate evaluation of the patient history was made to highlight a possible association with bisphosphonates (BF). The authors describe the cases of fractures associated with BF, in cases which showed a thickening of femoral cortex contralateral to the fracture site; these fractures were investigated with SPECT-Tc. The authors reviewed 319 Rxs of femoral fractures in patients over 60 who have had access to the PS of Clinical Orthopaedics and Traumatology II of the University of Pisa from January 2011 to February 2013.

According to Italian law, ethical approval for this study was not required because it involved only routine clinical follow-up and radiographic examination. Written informed consent was obtained from the patients. With this consent, the patient authorizes the surgical treatment and also the collection and publication of clinical data about his case for scientific and educational purposes even outside the institution.

The fractures were classified into three groups: medial fractures, lateral, and a third group including the subtrochanteric and diaphyseal fractures. Then, the fractures belonging to the third group were analyzed in details with the aim to select those that showed the radiographic criteria identification of atypical fractures. The atypical fractures have been investigated from clinical point of view, biohumoral exams, densitometry, and with the X-ray of the contralateral femur. In one case, in which there was a cortical thickening, a SPECT-Tc of the contralateral femur has also been executed.

## Results

Femoral fractures have been 319 in total: these fractures were divided into three groups: the medial fractures belong to the first group, the lateral ones belong to the second group, and subtrochanteric and diaphyseal fractures belong to the third group.

The medial femur fractures were 60 (46 females and 14 males), the lateral ones were 316 (237 females and 79 males). Subtrochanteric and diaphyseal fractures were 40 (29 females and 11 males). The mean age of patients was 83.13 years with a minimum age of 60 years and maximum of 104 years.

Among the fractures, belonging to the third group, those that present the major radiographic criteria for the definition of atypical fractures were three. Of these, one has proved to be a fracture secondary to a melanoma.

In the other two cases, there was an association with BF (Fig. 1). The two cases of atypical fracture were related to female patients, one was 79 years old and the other 77. In the first case, the patient had followed treatment with alendronate for 10 years, and in the second case, she had done risendronate therapy for 7 years.

In the first case, the patient had significant comorbidities such as systemic lupus erythematosus (SLE), venous insufficiency of the lower limbs with recurrent malleolar ulcers, and



**Fig. 1** X-ray exam of the pelvis at the time of arrival in the emergency department shows the left femur fracture

frequent episodes of TVP, autoimmune liver disease, dysplasia without blastosis, and bronchial asthma. The patient also had undergone cholecystectomy and electrical cardioversion after an episode of AF. Due to these diseases, the patient did the following therapies: corticosteroids since 1975, following of the diagnosis of LES anti-arrhythmic, proton pump inhibitor, immunosuppressants, and folic acid supplement.

In the second case, important comorbidities were not evidenced and the patient did not use drugs. This patient, about 4 months after hip fracture, fell down, reporting vertebral fractures.

In the case of patient with LES, the fracture was preceded by a period of nonspecific pain symptoms in the lower limb that was accentuated especially with the load.

In the case of the first patient, blood exams have shown the presence of hypovitaminosis D with values of 16.3 ng/ml (vn, 30–100), 45 U/L alkaline phosphatase (ALP) (vn, 35–105), 8.3 mg/dL Ca (vn, 8.6–10.2), and 42.8 pg/ml parathyroid hormone (PTH) (vn, 8–80). The densitometric values of the patient, measured approximately 4 months after the fracture, showed L1–L4 T-score of  $-1.7$ , and at the level of the femoral neck, T-scores were  $-0.3$  and  $-1.9$ .

In the case of the second patient, blood exams showed again hypovitaminosis D with values of 22.0 ng/ml (30–100 vn), 73 U/L ALP (vn, 35–105), 8.9 mg/dL Ca (vn, 8.6–10.2), and 57.2 pg/ml PTH (vn, 8–80). Densitometric values showed a worse clinical signs than the first patient with L1–L4 T-score of  $-3.0$  and T-score femur was  $-2.0$ . The patient was also submitted to ultradistal radio densitometry that showed a T-score of  $-2.7$ .

In both cases, it followed the same treatment protocol, according to the guidelines of the Task Force of the American Society for Bone and Mineral Research: the fracture was treated with intramedullary nailing (Fig. 2); the bisphosphonate therapy was suspended immediately, and it was replaced by teriparatide and supplementation with vit D [7].



**Fig. 2** The surgical treatment of the fracture with intramedullary nail

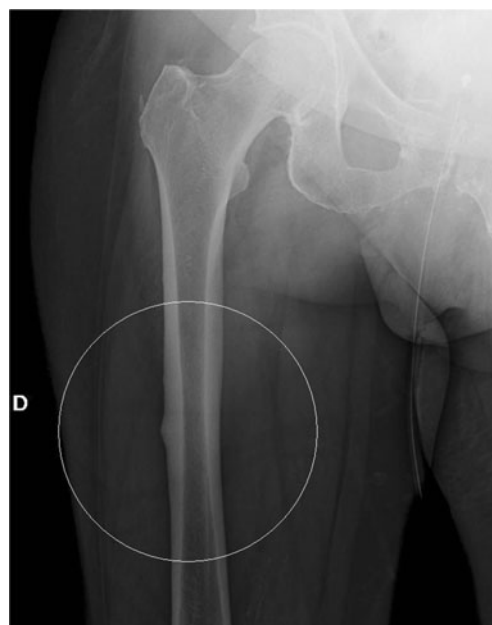
Both patients were subjected to x-rays of the contralateral femur respect of the fracture: in the first patient was highlighted a cortical thickening which had always been asymptomatic (Fig. 3). In this case we carried out a conservative treatment, with an initial unloading period, followed by a partial weight-bearing. Meanwhile the patient underwent to a SPECT-Tc which showed increased uptake at the 1/3 medium lateral cortex of the right femoral diaphysis. The patient underwent also to magnetotherapy at the level of the cortical thickening of the non-fractured side. The SPECT-Tc showed an increased uptake at the level of the maxillary and for this reason the patient completed dental examination which showed the presence of a granuloma and not a jaw osteonecrosis. The SPECT-CT showed the simultaneous presence of increased uptake at the level of the dorsal vertebrae D4–D5 and at the right humeral head.

In the second patient, the fracture is healed in proper time, while the second patient is still in the healing phase.

## Discussion

The etiopathogenetic mechanism underlying the onset of an atypical femoral fracture is not yet fully defined.

The most likely hypothesis is that posing like primary cause a decrease in bone remodeling. This would result in an accumulation of microdamage to the skeleton resulting in the impairment of the normal healing of micro-cracks by stress. This, in combination with an alteration of the mineral component and collagen induced by bisphosphonates would lead



**Fig. 3** The radiographic study of the right femur shows the cortical thickening

ultimately to an alteration of bone quality resulting in possible occurrence of atypical fractures. Radiographically, this is confirmed by cortical thickening, typical of stress fractures also in other districts, for example, the metatarsal fractures [12].

As a consequence, it can be hypothesized that the slow-down of the normal healing process induces a slowdown in the bone callus formation also and thus, may predispose to a nonunion until a pseudoarthrosis. [13]

Atypical fractures are rare events, extremely subtle and often unrecognized, may be bilateral, and seem to have a worse prognosis respect of “typical” fractures. A careful assessment of patients treated by bisphosphonates is therefore necessary, especially if protracted for a long time, for a correct diagnosis, and for an appropriate treatment setting.

Knowing that the usefulness of bisphosphonates in reducing the risk of fractures exceeds the occurrence of atypical fractures [14] and despite the low incidence of atypical fractures associated with bisphosphonates, these pathologies are to be considered due to the large use of these drugs in the prevention of fragility fractures.

This kind of fracture is an insidious disease that often affects the femur bilaterally. It seems that the “atypical” fractures are predisposed to a delay of healing if compared to the “typical” fragility fractures [15, 16]. Moreover, in the literature, there are case reports of atypical fractures that occur to other skeletal areas in addition to femur.

Their incidence is correlated with the time of treatment, and to date, the limit of “safe use” of BF is 5 years. However, a case exists in the literature that reports the occurrence of a fracture atypical after 16 months of treatment. The dose of the drug instead does not seem to be correlated with the incidence of fractures.

Discontinuation of therapy results in a reduction of fracture risk which, however, does not end with an on–off phenomenon but remains a therapeutic tail that is in relation to the “duration of effect” of the drug on the bone. In particular, it is estimated that the therapeutic tail of alendronates is 1.2 years while for the risendronate is 3.5 years.

At present, it is difficult to define the true incidence of atypical fractures associated with bisphosphonate because studies are retrospective, and there is no diagnostic code ICD-9 identification for this disease. However, our case study seems to indicate that the incidence of atypical fractures is higher than that reported in the literature when compared to “typical” fractures that occurred in the same anatomical site.

All the data in the literature about the incidence of atypical femoral fractures refer to all fractures of the femur, including both medial fractures, lateral fractures, and diaphyseal ones. In our review, the incidence of atypical fractures is 0.6 %, according to data from the most recent literature. However, the authors emphasize that considering only the fracture locations suitable for the identification of atypical fractures, to say, from below

the lesser trochanter to those supracondylar, the percentage rises to 5 %, figure that asks for additional investigation for the proper framing of this type of fracture.

To date, there is still no clarity on the exact etiology of fractures even if it seems to be related to a bone mineral component alteration.

**Conflicts of interest** None.

## References

- Gradi MK, Watson JT, Cannada LK (2012) Treatment of femoral fracture nonunion after long-term bisphosphonate. *Orthopedics* 35(6):e991–995
- American College of Rheumatology (2001) Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheum* 44:1496–1503
- Cranney A, Tugwell P, Adachi J, Weaver B, Zytaruk N, Papaioannou A et al (2002) Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. *Endocr Rev* 23:517–523
- Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V et al (2002) Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev* 23:508–516
- Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY (2005) Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab* 90(3):1294–1301
- Lenart BA, Lorich DG, Lane JM (2008) Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N Engl J Med* 358(12):1304–1306, 20
- Annunziata A, Unnanuntana A, Saleh A, Mensah KA, Kleimeyer JP, Lane JM (2013) Atypical femoral fractures: what do we know about them? *J Bone Joint Surg Am* 95:e8 (1–13)
- Abrahamsen B, Eiken P, Eastell R (2009) Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. *J Bone Miner Res* 24: 1095–1102
- Giusti A, Hamdy NAT, Dekkers OM, Ramautar SR, Dijkstra S, Papapoulos SE (2011) Atypical fractures and bisphosphonate therapy: a cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features. *Bone* 48: 966–971
- Girgis CM, Seibelet MJ (2011) Atypical femur fractures: a review of the evidence and its implication to clinical practice. *Ther Adv Musculoskelet Dis* 3(6):301–314, 011 Dec
- Compston J (2011) Pathophysiology of atypical femoral fractures and osteonecrosis of the jaw. *Osteoporos Int* 22:2951–2961. doi:10.1007/s00198-011-1804-x
- Mashiba T et al (2011) Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. *Bone* 28(5): 524–531
- Carvalho NNC, Voss LA et al (2011) Atypical femoral fractures during prolonged use of bisphosphonates: short-term responses to strontium ranelate and teriparatide. *J Clin Metab*. doi:10.1210/jc.2011-0593
- Dell RM, Adams AL, Greene DF, Funahashi TT, Silverman SL, Eiseimon EO, Zhou H, Burchette RJ, Ott SM et al (2012) Incidence of atypical nontraumatic diaphyseal fractures of the femur. *J Bone Miner Res* 27(12):2544–2550

15. Giannotti S, Bottai V, Dell'Osso G, De Paola G, Ghilardi M, Guido G (2013) Pseudoarthrosis in atypical femoral fracture: case report. *Osteoporos Int*. doi:[10.1007/s00198-013-2397-3](https://doi.org/10.1007/s00198-013-2397-3)
16. Giannotti S, Bottai V, Dell'Osso G, De Paola G, Pini E, Guido G (2012) Atrophic femoral nonunion successfully treated with teriparatide. *Eur J Orthop Surg Traumatol*. doi:[10.1007/s00590-012-1143-4](https://doi.org/10.1007/s00590-012-1143-4)