# Atypical fractures of proximal femur associated with prolonged use of bisphosphonates

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## Abstract

**Introduction:** Biphosphonates are the treatment of first choice for the osteoporotic disease. Some adverse effects, such as atypical proximal femur fractures, call biphosphonates prolonged use into question. The aims of this study are to determine the relationship between biphosphonates use and atypical femur fractures, and to show such fractures at our institution.

**Materials and Methods:** Observational, retrospective study—unpaired case-control analysis. We included > 55 year-old patients with femur fracture admitted between January 1st 2009 and May 31st 2015. Variables considered were: sex; age; type of fracture; use, type and time of biphosphonate use. Fractures were classified as typical—interthrocanteric and medial fractures; and atypical—subthrocanteric and diaphyseal fractures. We took atypical fractures as cases and interthrocanteric fractures as controls.

**Results:** We included 517 patients who met the inclusion criteria. Forty-two fractures were atypical and 236, typical. The female sex prevailed (81.4% in the cases and 83% in the controls). Patients averaged 76 and 80 years old, respectively. The association with biphosphonate use was 44.2% in the cases and 15.3% in the controls (11.6% and 0.8% in the interthrocanteric fractures, respectively).

**Conclusions:** Alendronic acis was significantly associated with femur atypical fractures. We did not find any association with time of use; however, incidence was higher after 4.5 to 5 years of use.

**Key words:** Hip fracture; osteoporosis; biphosphonates.
**Level of evidence:** IV

### Fracturas atípicas de fémur proximal asociadas al uso prolongado de bifosfonatos

## Resumen

**Introducción:** Los bifosfonatos constituyen el tratamiento de primera elección de la enfermedad osteoporótica. Algunos efectos adversos ponen en duda su uso prolongado, como las fracturas atípicas de fémur proximal. Los objetivos de este estudio fueron determinar la relación entre consumo de bifosfonatos y fracturas atípicas de fémur, y mostrar la incidencia en nuestra institución.

**Materiales y Métodos:** Estudio retrospectivo, observacional, análisis de caso-control no pareado. Se incluyeron pacientes >55 años, con fractura de fémur que ingresaron entre el 1 de enero de 2009 y el 31 de mayo de 2015. Las variables consideradas fueron: sexo, edad, tipo de fractura; uso, tipo y tiempo de consumo de bifosfonatos. Las fracturas se distribuyeron en típicas: pertrocantéricas, y cuello femoral, y atípicas: subtrocantéricas y diafisarias. Se consideraron como casos las fracturas atípicas y como controles, las pertrocantéricas.

Conflict of interests: The authors have reported none.

**Resultados:** Se incluyó a 517 pacientes que cumplieron los criterios de inclusión. Cuarenta y dos fracturas eran atípicas y 236, típicas. Hubo predominio del sexo femenino (81,4% en los casos y 83% en los controles). La edad promedio fue de 76 y 80 años, respectivamente. La asociación con bifosfonatos fue del 44,2% en los casos y 15,3% en los controles (11,6% y 0,8% en las fracturas pertrocantéricas, respectivamente).
**Conclusiones:** El alendronato se asoció significativamente con fracturas atípicas de fémur. No se halló relación con el tiempo de consumo; sin embargo, la incidencia fue más alta luego de 4.5-5 años de consumo.

**Palabras clave:** Fractura de cadera; osteoporosis; bifosfonatos.
**Nivel de Evidencia:** IV

## Introduction

Nowadays, biphosphonates are considered to be the treatment of first choice for the osteoporotic disease. Their recognized anti-fracture efficiency in all kinds of osteoporosis and their presence in the market for a number of years already make them the most widely used drugs. A series of adverse effects related to biphosphonates has raised alarm calls to warn of danger of long-term continuous treatment, though. There are reports on atypical fractures, especially proximal femur fractures considered as such due to their location and radiologic looks which do not meet the classical criteria for fragility fracture (osteoporotic disease).[1] Prolonged inhibition against bone remodeling might represent the pathophysiological foundations for this, although this causal relationship has not been established yet.

The aims of this study were to determine the relationship between chronic use of biphosphonates and atypical femur fractures, to assess the correlation between the time biphosphonates have been administered and the fracture event, and to propose an algorithm for the follow-up on patients with chronic biphosphonates use so as to detect the cases of potential risk of atypical fracture. We also carried out a bibliographic revision.

## Materials and Methods

Observational, retrospective study—unpaired case-control analysis. We included patients undefined by sex, >55 years old, with diagnosis of hip fracture/proximal femur fracture who were admitted to the Orthopedics Department at the Hospital Público Universitaro of Córdoba between January 1st 2009 and May 31st 2015. The assessed variables were: sex, age, type of fracture, use of biphosphonates, type and time of use, type of traumatism, comorbidities, associated drugs and osteoporosis diagnosis by DEXA. Fractures were classified by location as: Typical fractures—hip interthrocanteric fracture and neck fracture, and Atypical fractures—subthrocanteric fractures and proximal/mid/distal-third diaphyseal femur fractures with history of low-energy traumatism or spontaneous onset.

Exclusion criteria were <55 year-old patients, high-impact fractures in the context of politraumatism, pelvic fracture and peri-prosthetic fracture. We took atypical fractures as cases and typical fractures as controls. Variables were summarized in terms of frequency, media and standard deviation (SD). We carried out bivariate analyses, multivariate analyses, t-tests and logistic regression analyses. Significance was considered to be $p<0.05$ with 95% confidence interval.

## Results

We revised 767 electronic medical histories of patients with hip fracture (occurring over a period of 6 years and 5 months); 517 met the inclusion criteria. Fractures were: interthrocanteric fractures (45.7%; n= 236), neck fractures (43.3%; n= 224), proximal and mid-diaphyseal femur fractures (4.6%; n= 24), subthrocanteric fractures (3.7%; n= 19) and distal diaphyseal femur fractures (2.7%; n= 14).

Eventually, the case/control analysis included 279 fractures: 43 atypical fractures and 236 typical fractures. The female sex prevailed: 81.4% (35/43) in the cases and 83% (196/236) in the controls. The average age was 76 years old (9.3 SD) and 80 years old (8.7 SD), respectively (p= 0.00) (OR= 0.9). In the bivariate analysis, the association with biphosphonates was 44.2% (19/43) in the cases and 15.3% (36/235) in the controls (p= 0.00), what remained in the multivariate analysis with an OR= 3.6. Alendronic acid was the only type of biphosphonate which had a significant association with atypical fractures, 11.6% (5/43), and it was associated in 0.8% (2/235) with typical fractures (p=0.00). The atypical fractures were mainly non-traumatic (53.5%; 23/43) vs. 9.3% (22/235) in the typical fractures (22/235), with statistical significance (p=0.000). In the bivariate analysis of comorbidities, atypical fractures were associated with osteoporosis (55.8%; 24/43 of the cases and 17%; 40/235 of the controls) (p=0.00), with autoimmune disease (9.3%; 4/43 and 1.7%; 4/236, respectively) (p=0.00) and with the use of corticosteroids (18.6%; 8/43 and 5.5; 13/236, respectively) (p=0.003).

At the time of carrying out the multivariate analysis, the only association that remained was that of atypical frac-

ture with osteoporosis (5.5 % OR). Forty-three percent (18/42) of the cases and 17% (38/229) of the controls had undergone DEXA (p=0.000). We did not find differences in the years of use of biphosphonates between atypical fractures (5.11) and typical fractures (4.41) (p=0.08).

## Discussion

Biphosphonates ara anti-osteoporotic drugs highly efficient in the prevention of vertebral and non-vertebral fractures. The incidence of atypical proximal femur fractures in the patients treated with biphosphonates is relatively low. The reduction of the risk ranges from 40% to 70% for vertebral fractures and from 40% to 50% for femur fractures.[2] Among all the complications that have been described, the one that has raised alarm calls and call long-term biphosphonate treatment into question has been the progressively increasing rates of atypical femur fracture. From the pathophysiological point of view, prolonged biphosphonate treatment implies excessive suppression of bone remodeling, what in turn may imply greater mineralization, accumulation of aged bone without remodeling and, therefore, greater risk of microfracture. However, it is not possible to establish a causal relationship between prolonged biphosphonate treatment and atypical fractures, and it is likely that such drugs play a role in the development of atypical fractures together with *other* causal factors.

The incidence of atypical femur fractures increases as time of exposure to biphosphonates does. They can be uni- or bilateral, complete or incomplete, and they usually involve a transverse or slightly oblique line, a non-comminuted pattern and the formation of a characteristici medial spike. In the vast majority of cases, there is lateral cortex thickening. In the case of a patient who receives prolonged biphosphonate treatment and reports continuous groin or thigh pain with no history of high-energy impact, and in all the cases of complete or incomplete unilateral atypical fracture, with or without symptoms, doctors are advised to ask patients simple contralateral femur anteroposterior/lateral X-rays including the whole of the femur diaphysis.[3] If this study is not conclusive enough and there is high level of clinical suspicion, the indication

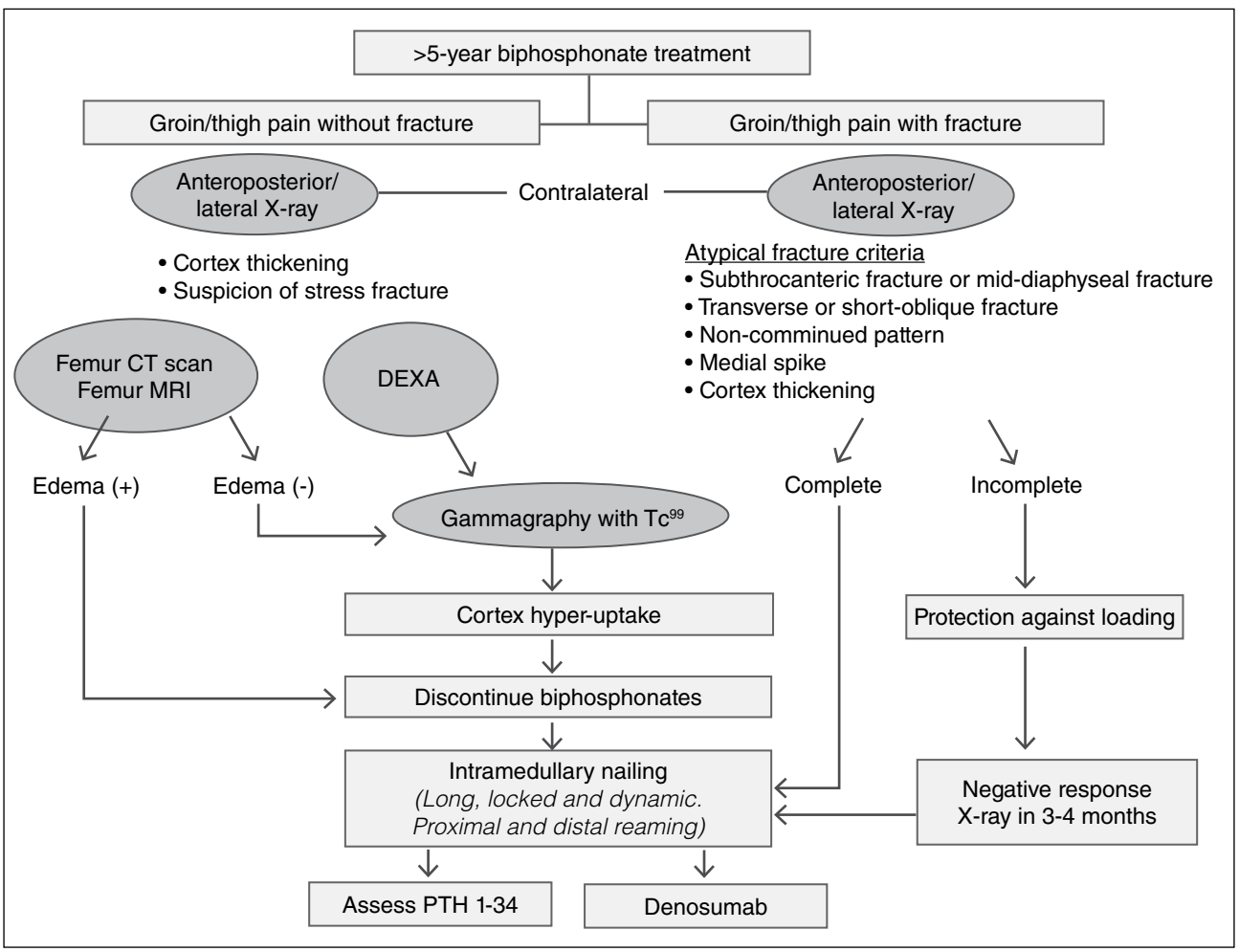


**Figure 1.** Diagnostic and therapeutic algorithm for atypical fractures associated with prolonged use of biphosphonates.

may be CT scan, MRI or gammagraphy of the contralateral femur in search of predictive signs of failure fracture or developing stress fracture (Figure 1).

These fractures require efficient ostoesynthesis by intrameullary nailing with reamed long nail that prevents the whole femur diaphysis from re-fracturing. Especially in incomplete atypical fractures with thigh pain, if they do not respond to conservative treatment, the indication may be prophylactic intramedullary nailing.

Nowadays the general incidence of femur subthrocanteric fracture and femur mid-diaphyseal fracture associated with low-energy traumatism is estimated to range between 2 and 4% in all hip fractures. Seventy-five percent of these types of fractures are usually associated with high-energy traumatisms. The impacts that these fractures make in terms of morbimortality is comparable with each other, however, with mortality rates of 12% at postoperative month 12, and 25% at postoperative month 24, and with such functional effects that most patients (71%) are not able to retake daily activities as they used to carry them out before undergoing surgery.

At the time of evaluating more specifically the epidemiology of failure or stress subthrocanteric fractures, which occur under specific bone metabolic circumstances due to deficiency in bone elastic-plastic resistance, there is a prevalence of about 1% of such fractures that does not vary. Approximately 25% of all femur subthrocanteric and diaphyseal fractures are believed to have characteristics that allow us to define them as atypical fractures associated with prolonged use of biphosphonates.

Therefore, the incidence of atypical fractures associated with prolonged use of biphosphonates seems to be very low, not only while comparing them directly with the number of femur subthrocanteric or diaphyseal fractures in general but also while comparing them indirectly with the number of vertebral, non-vertebral and hip fractures prevented by such drugs. However, independently of the data from the most updated bibliography about the chronic use of biphosphonates in association with the risk of atypical fractures, at our institution, there were 8.3% of atypical fractures out of which 11.6% was associated with chronic use of biphosphonates (> 4 years).[4]

With respect to the indications and the prescription of biphosphonates to treat the osteoporotic disease, we use the diagnostic protocols that are based on the results of the DEXA, for which the WHO sets a T-score inferior to -2.5 and risk factors in the context of the patient's personal pathologic history as standard diagnosis references.[5] Such criteria are based on the ultimate *Guías 2012 para el Diagnóstico, Prevención y Tratamiento de la Osteoporosis* (2012 guidelines for diagnosis, prevention and treatment of osteoporosis) issued by the *Asociación Argentina de Osteología y Metabolismo Mineral* and the *Sociedad Argentina de Osteoporosis* (Argentine association of osteology and mineral metabolism and Argentine society of osteoporosis).

Nowadays, in consonance with available bibliography, biphosphonates are still the standard treatment for osteoporosis. The decision of starting an osteoporosis treatment with biphosphonates should be made on an absolutely individual basis and be based on an appropriate assessment of the risk/benefits ratio it is associated with. Although apparently patients treated with biphosphonates benefit from considerable decrease in their risk of fracture during at least five years, continuous biphosphonate use should be reassessed on a yearly basis. For those patients whose fracture risk remains moderately high, treatment should definitely continue. However, low-risk patients, those who do not show recent fracture or DEXA osteoporosis (>2.5 T-score), after the initial therapeutic course may benefit from "therapeutic holidays".[6]

In order to clearly establish patients' risks of suffering these fractures and their potential relationship with biphosphonate treatment, well-designed, prospective studies are required. It is necessary to create specific diagnostic codes to facilitate their records, to promote their study and to establish an adequate medical-clinical management.

Moreover, it is necessary to clearly individualize secondary osteoporosis by assessment of phosphor-calcium metabolism, paying special attention to Vitamin D deficits and correcting them by adequate supplementation. Specialized bibliography offers multiple alternative therapeutic options for osteoporosis, along with treatments to keep normal levels of calcium and Vitamin D; they are mostly based on very-expensive teriparatide treatment, and treatments with monoclonal antibodies such as denosumab.[7]

## Conclusions

The decision to start treatment with biphosphonates results from a complex evaluation of their cost/benefit ratio based on the assessment of the risk factors they are associated with.

Alendronic acid is the only biphosphonate which was significantly associated with atypical proximal femur fractures. We did not find any association with time of use, probably due to lack of data in electronic medical histories; however, there is a greater tendency at more than 4.5 to 5 years of use.

It is estimated that the reduction of non-vertebral fracture risks due to alendronic acid treatment in patients without previous fracture is 30%.[8] After five years of treatment, continuing for other five years lowered the incidence of vertebral fractures in 45% as compared with patients who had received active treatment but who had then discontinued treatment. The absolute reduction of risks was 2.4% due to the low number of patients with fracture.

In view of the lack of follow-up protocols for patients with chronic use of biphosphonates, this study shows an algorithm of therapeutic measures and biochemical plus imaging studies that are necessary to timely detect patients with risk of suffering atypical fractures (Figure 2). Nevertheless, according to our bibliographic revision, the pathophysiology underlying this pathologic association as adverse effect is still to be found out.

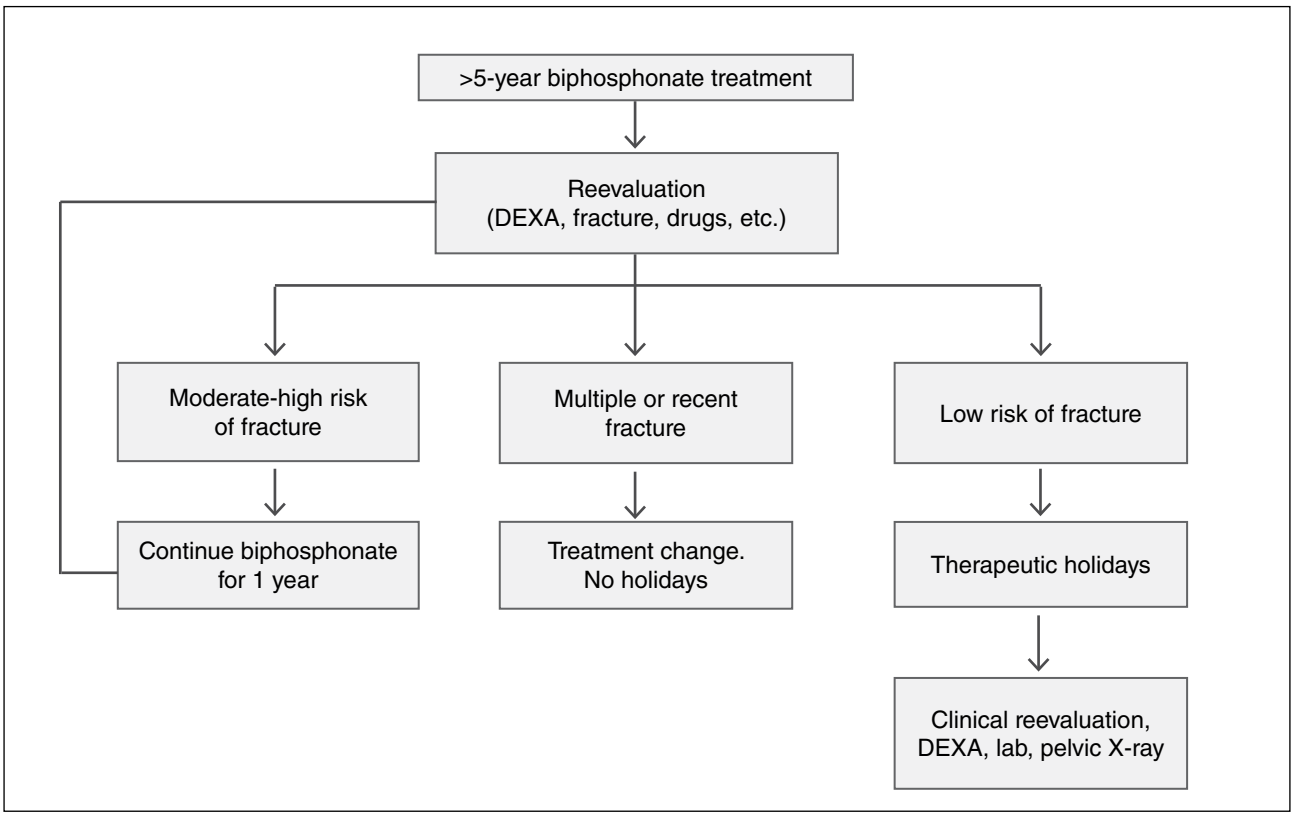


**Figure 2.** Follow-up algorithm for biphosphonate treatment.

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