

Atypical Femoral Fractures and Bisphosphonates Treatment: Is it a Risk Factor?



Fracturas Femorais Atípicas e o Tratamento com Bifosfonatos: É um Factor de Risco?

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 Acta Med Port 2014 Nov-Dec;27(6):704-709

ABSTRACT

Introduction: Bisphosphonates are effective in preventing osteoporotic fracture, however atypical femoral fractures with a well-defined radiological pattern have been described in association with prolonged treatment with bisphosphonates. Our objectives in this study were to characterize patients ≥ 65 years old with femoral fractures (subtrochanteric/diaphyseal) considered typical and atypical and the relationship between the occurrence of atypical fractures and bisphosphonate use.

Material and Methods: We conducted a case-control study with patients admitted in our hospital with subtrochanteric or diaphyseal femur fracture in a period of five and a half years. After applying the exclusion criteria, the 92 fractures (91 patients) were classified as typical or atypical. The determination of prior bisphosphonate treatment was obtained through consultation of the individual medical history.

Results: We found 11 atypical fractures (10 patients) and 81 typical fractures (81 patients). The median age of both groups was statistically different (72 years - atypical vs. 80 years - typical, $p < 0.01$). The reason for the use of bisphosphonates was 0.60 in atypical fractures and 0.01 in typical, and an odds ratio of 101.1 was obtained ($p < 0.01$).

Discussion: Our results are supported and are in agreement with published studies relating to the occurrence of atypical femoral fractures associated with treatment with bisphosphonates.

Conclusion: Despite the small number of cases it was possible to demonstrate a statistically significant relation between atypical femoral fractures and treatment with bisphosphonates. One should note that these atypical fractures occurred in patients significantly younger than patients with typical fractures.

Keywords: Diphosphonates; Femoral Fractures; Risk Factors.

RESUMO

Introdução: Os bifosfonatos têm eficácia comprovada na prevenção das fracturas osteoporóticas. Contudo, têm sido descritas fracturas femorais atípicas associadas à toma prolongada de bifosfonatos com um padrão radiológico bem definido. Os objectivos no nosso estudo foram caracterizar os doentes de idade ≥ 65 anos com fracturas femorais (subtrocantericas/diafisárias) consideradas típicas e atípicas e avaliar a relação entre a ocorrência das fracturas atípicas e o uso de bifosfonatos.

Material e Métodos: Realizámos um estudo caso-controlo com os doentes admitidos no nosso Hospital por fractura subtrocanterica ou diafisária do fémur, num período de cinco anos e meio. Após aplicação dos critérios de exclusão, as 92 fracturas (91 doentes) foram classificadas como atípicas ou típicas. A determinação do tratamento prévio com bifosfonatos foi obtida através do historial clínico dos doentes.

Resultados: Foram encontradas 11 fracturas atípicas (10 doentes) e 81 fracturas típicas (81 doentes). A idade mediana entre os dois grupos foi estatisticamente diferente (72 anos - atípicas vs 80 anos - típicas, $p < 0,01$). A razão do uso de bifosfonatos foi de 0,60 nas fracturas atípicas e de 0,01 nas típicas, traduzindo um odds ratio de 101,1 ($p < 0,01$).

Discussão: Na generalidade, os nossos resultados são apoiados e estão de acordo com os estudos publicados referentes à ocorrência de fracturas femorais atípicas associadas à toma de bifosfonatos.

Conclusão: Apesar do pequeno número de casos foi possível demonstrar a relação, estatisticamente, significativa entre as fracturas femorais atípicas e a toma de bifosfonatos. De notar que estas fracturas atípicas ocorreram em doentes, significativamente, mais jovens do que os doentes com fracturas típicas.

Palavras-chave: Difosfonatos; Fracturas do Fémur; Factores de Risco.

INTRODUCTION

Bisphosphonates have proven to be effective in the treatment of osteoporosis and in prevention of typical osteoporotic fractures.¹⁻³ However, some atypical subtrochanteric or diaphyseal femoral fractures were described and studies were published associating these to long-term bisphosphonate use,⁴⁻⁶ namely beyond five years,⁷ due to a probable inhibition of bone regeneration.^{8,9} There are even studies relating atypical femoral fractures to shorter-term use (< 2 years).⁵ The inhibition of bone regeneration capacity seems to also affect fracture healing leading to the need for subsequent treatment in some patients.⁹

These atypical femoral fractures are related to minimal trauma and show a well-defined radiographic pattern: transverse fracture line orientation, external cortical thickness, the presence of a medial spike and minimally comminuted fractures.^{8,10}

This is a controversial issue, as there are also studies showing no association between the use of bisphosphonate and atypical femoral fractures.¹¹

We are not able to study the dimension of this problem in Portugal, as we can only find national studies describing individual case-reports.

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Recebido: 29 de Dezembro de 2013 - Aceite: 19 de Março de 2014 | Copyright © Ordem dos Médicos 2014



Our study aimed to characterize the patients aged 65 or above presenting with femoral (subtrochanteric and diaphyseal) fractures classified as atypical and to evaluate the relationship between the occurrence of an atypical fracture and the use of bisphosphonates.

MATERIAL AND METHODS

Design and population

A case-control study was carried out involving all the patients aged 65 or above admitted to our Hospital with femoral subtrochanteric or diaphyseal fractures occurring between the 1st January 2008 and the 30th June 2013 (data were collected between the 17th July 2013 and the 2nd September 2013).

The patients with high-energy (related to traffic accidents or falls from standing height or above), repetitive fractures (peri-prosthetic fractures) or with known neoplasms were excluded.

Data source

The 'femoral subtrochanteric or diaphyseal fracture' events were obtained through a search at our Hospital's Clinical Codification Department (*Gabinete de Codificação Clínica*) using the 82022 and 82101 codes of the International Disease Classification – Ninth Revision. The events and the type of fracture were confirmed through the analysis of the clinical record and examination of the digital radiography obtained at the time of the fracture. The clinical record was examined at the Clinical Archive and using the *Sistema de Apoio ao Médico (SAM)* software; the examination of the digital radiography was performed through the CARESTREAM Vue PACS software used for the Hospital's imaging archive. It has been in place since 2008, justifying why our study started on that year.

Case and control definition

Ninety-one patients met the inclusion criteria and subtrochanteric ($n = 80$) or diaphyseal ($n = 12$) femoral fractures were classified as atypical (cases) or typical (controls) fractures according to the observation of the digital radiographies made by the authors without prior knowledge of each patient's clinical data. In the event of a difference between radiography evaluations, the conclusion was reached through consensus between the authors.

The atypical fracture classification (cases) was based on the reviewed criteria for case definition of atypical femoral fractures published by the American Society for Bone and Mineral Research⁸: associated to minimal or no trauma, predominantly transverse configuration, generalized increase in cortical thickness of the diaphysis, associated with a medial spike and minimally comminuted. The fractures that were not included in previously defined criteria were classified as typical fractures (controls).

Exposure evaluation

Prior bisphosphonate treatment at the time of the fracture was determined through patient's direct interviews, the

clinical record, SAM's data and national prescription data obtained at the *Plataforma de Dados da Saúde* database. Data regarding the specific drug, treatment starting date and duration were obtained for the patients on bisphosphonate.

Statistical analysis

A descriptive analysis of both groups was carried out (age, gender, type of fracture and bisphosphonate treatment) using Microsoft Excel® database.

The Wilcoxon's test was used to compare the median age in both groups.

The association between atypical fracture and bisphosphonate use was evaluated and the odds ratio was calculated through Fisher's exact test, according to our patient's characteristics.¹²

The differences among groups were considered as statistically significant when the p value was <0.05 .

Wilcoxon's tests and odds ratio were obtained through the R software, version 3.0.2 (<http://www.R-project.org/>).¹³

RESULTS

From the 112 patients aged 65 or above, admitted between the 1st January 2008 and the 30th June 2013 diagnosed with a subtrochanteric or diaphyseal femoral fracture, 91 patients met the inclusion criteria, corresponding to 92 fractures (Fig. 1). From these, we found 11 atypical fractures in 10 patients (one patient presented with a simultaneous bilateral fracture) and 81 typical fractures in 81 patients. All the fractures were treated with intramedullary rod placement.

The group of atypical fractures included three diaphyseal and eight subtrochanteric fractures. In this group, the median age was 72 (65-80), including only female patients (Table 1). The group of typical fractures included nine diaphyseal and 72 subtrochanteric fractures. In this group, the median age was 80 (65-99) including mostly female patients (83.9%). The median age was considered as statistically different (72 vs. 80 years, $p < 0.01$).

The use of bisphosphonate was recorded in six patients with atypical fractures, with five-year median treatment duration. We did not find any bisphosphonate use in the remaining four patients with atypical fractures. In the typical fracture group, the use of bisphosphonates was only found in one patient (Table 2). Alendronate was the bisphosphonate prescribed for all the patients. A 0.60 hazard ratio was obtained for the use of bisphosphonate in patients with atypical fractures and a 0.01 hazard ratio in patients with typical fractures. A 101.1 odds ratio (95% confidence interval; 9.5 to 5,326.2; $p < 0.01$) was obtained, which is statistically significant.

On a second analysis adjusted to the patients split between <5 year or ≥ 5 year bisphosphonate use (Table 3), an infinite odds-ratio was obtained (95% Confidence Interval; 6.76 to infinite; $p < 0.01$), which is statistically significant.

The presence of prodromal symptoms was only described in a 65-years-old patient under long-term

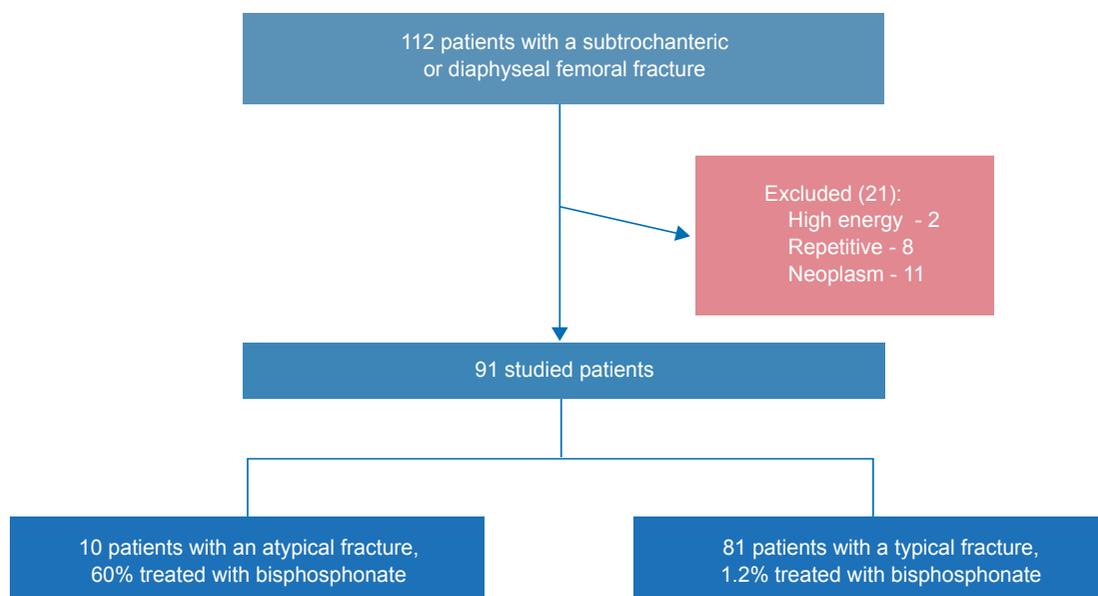


Figure 1 - Patients selection

Table 1 - Patient characterisation according to the type of fracture (typical vs. atypical)

Variável	Patients with fracture, n (%)	
	Atypical (n = 10)	Typical (n = 81)
Side		
Right	2 (20.0)	40 (49.4)
Left	7 (70.0)	41 (50.6)
Bilateral	1 (10.0)	0 (0.0)
Use of bisphosphonate		
Alendronate	6 (100.0)	1 (100.0)
Duration of treatment (years)		
No use	4 (40.0)	0 (0.0)
< 5	2 (20.0)	1 (1.2)
5-10	3 (30.0)	0 (0.0)
> 10	1 (10.0)	0 (0.0)
Female	10 (100.0)	68 (83.9)
Age (years)		
65-69	3 (30.0)	7 (8.6)
70-74	5 (50.0)	16 (19.8)
75-79	1 (10.0)	14 (17.3)
80-84	1 (10.0)	20 (24.7)
85-89	0 (0.0)	19 (23.5)
90-95	0 (0.0)	1 (1.2)
95-99	0 (0.0)	4 (4.9)

bisphosphonate use (>10 years) and with simultaneous bilateral atypical fracture (Fig. 2).

DISCUSSION

The results of our study are globally in line with what has been published regarding atypical femoral fractures.

Atypical fractures represented 11% of subtrochanteric

Table 2 - Patient characterisation according to the type of fracture (typical vs. atypical) and bisphosphonate use

	Patients with atypical fracture (n = 10)		Patients with typical fracture (n = 81)	
	Use of bisphosphonate, n (%) (n = 6)	No use of bisphosphonate, n (%) (n = 4)	Use of bisphosphonate, n (%) (n = 1)	No use of bisphosphonate, n (%) (n = 80)
Female	6 (100.0)	4 (100.0)	1 (100.0)	67 (83.8)
Age				
65-69	3 (50.0)	0 (0.0)	0 (0.0)	7 (8.8)
70-74	3 (50.0)	2 (50.0)	0 (0.0)	16 (20.0)
75-79	0 (0.0)	1 (25.0)	0 (0.0)	14 (17.5)
80-84	0 (0.0)	1 (25.0)	1 (100.0)	19 (23.3)
85-89	0 (0.0)	0 (0.0)	0 (0.0)	19 (23.3)
90-95	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
95-99	0 (0.0)	0 (0.0)	0 (0.0)	4 (5.0)
Corticosteroid therapy	0 (0.0)	2 (50.0)	0 (0.0)	1 (1.3)

Table 3 - Patient characterisation according to the type of fracture (typical vs. atypical) and duration of bisphosphonate use (< 5 vs. ≥ 5 years)

	Patients with atypical fracture (n = 10)		Patients with typical fracture (n = 81)	
	Use of bisphosphonate ≥ 5 years, n (%) (n = 4)	No use/Use of bisphosphonate < 5 years, n (%) (n = 6)	Use of bisphosphonate ≥ 5 years, n (%) (n = 0)	No use/Use of bisphosphonate < 5 years, n (%) (n = 81)
Female	4 (100.0)	6 (100.0)	0 (100.0)	68 (83.9)
Age				
65-69	3 (75.0)	0 (0.0)	-	7 (8.6)
70-74	1 (25.0)	4 (66.7)	-	16 (19.8)
75-79	0 (0.0)	1 (16.7)	-	14 (17.3)
80-84	0 (0.0)	1 (16.7)	-	20 (24.7)
85-89	0 (0.0)	0 (0.0)	-	19 (23.5)
90-95	0 (0.0)	0 (0.0)	-	1 (1.2)
95-99	0 (0.0)	0 (0.0)	-	4 (4.9)

and diaphyseal femoral fractures in our study, a rate similar to that found by Thompson *et al.*,⁴ Meier *et al.*⁵ and Park-Wyllie *et al.*,⁷ with 7, 8 and 11% rates, respectively.

The median age at the time of an atypical fracture (72 years) was statistically lower than the median age of typical fractures. Although a direct comparison is not possible, this age distribution seems to be in line with the study by Meier *et al.* that found a median age of atypical fractures in the 70-79 group and typical in the 80-89 age group.⁵ Also according to

this author, female gender represents most patients in both cases, mostly with atypical fractures (92% vs. 72%, atypical vs. typical).⁵ This distribution is also in line with our study, with 100% female patients with atypical fractures and 84% in female patients with typical fractures.

The use of bisphosphonate was found in six (60%) of the 10 patients with an atypical fracture. This rate was in line with what was found by Park-Wyllie *et al.*⁷ and below the rate found by Thompson *et al.*¹⁴ and Meier *et al.*,⁵ with

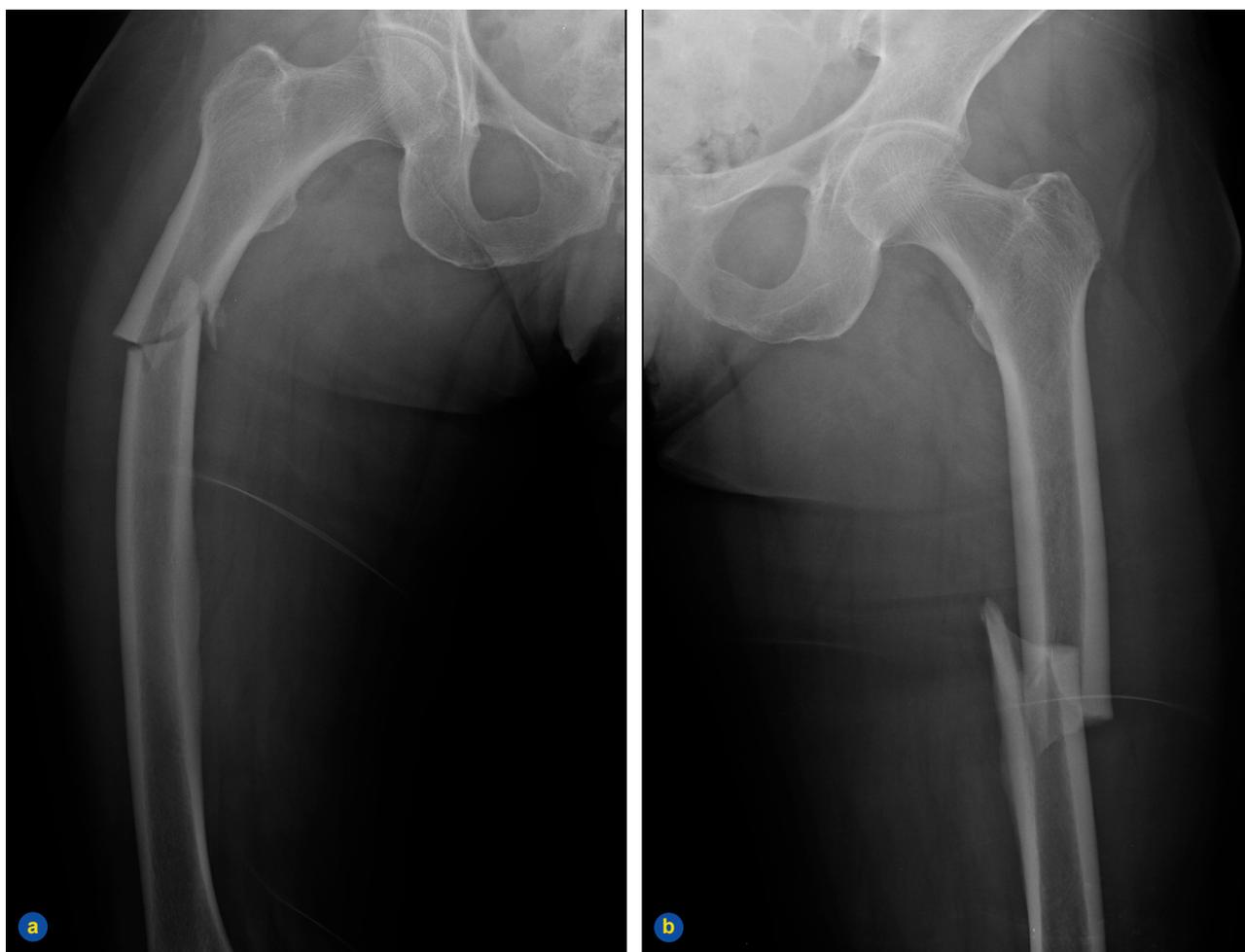


Figure 2 - Radiograph of the right (A) and the left thigh (B) of a patient with simultaneous bilateral fracture and in treatment with bisphosphonate. We wish to emphasize the presence of atypical characteristics in both fractures.

64%, 81% and 92%, respectively.

The occurrence of an atypical fracture seems to be associated to the use of bisphosphonate, according to the odds ratio of 101.1 obtained in our study (a statistically significant result) in a group of patients with five-year median treatment duration. These results are in line with literature, with 9.46 odds ratio in patients treated for more than three years (Erviti *et al.*)¹⁵, 66.9 in patients with 5-9 year median duration of treatment (Meier *et al.*)⁵ and 1,000 in patients with a 7.1-year average treatment (Isaacs *et al.*)⁶ results that also are statistically significant and with 95% confidence intervals.

Regarding the presence of prodromal symptoms, Isaacs *et al.* found 71% of the patients with pain three-weeks to six-months before the fracture (average treatment of 7.1 years).⁶ The same author recommends the suspension of the use of bisphosphonate beyond five years and an active search for prodromal symptoms and radiologic monitoring in clinical practice. In our population, the presence of prodromal symptoms was only described by one patient with a simultaneous bilateral atypical fracture.

The strengths of our study include the radiographic separation of the patients in two groups (cases – atypical vs. controls – typical fracture) blinded to the patient's clinical

data and the inclusion of all eligible patients diagnosed with subtrochanteric and diaphyseal femoral fractures.

The major limitations of our study include its retrospective nature, the possibility of incomplete clinical records; the absence of known factors related to bone mass changes like body mass index, non-actively researched data regarding gynaecology history or medication and the small number of patients, which relates to the rarity of the clinical event.

Our study leaves raises some issues, the most important of which is the cause for atypical fractures in patients without any prior bisphosphonate use. We found in our study that four of 10 patients (40%) with this type of fracture had no past history of bisphosphonate use. From these, only two were diagnosed with rheumatoid arthritis under corticosteroid therapy, which may have contributed to bone fragility but the remaining two fractures remain to be explained. Further studies are needed to globally understand this clinical situation.

CONCLUSION

Despite the small number of patients, we were able to show a statistically significant relationship between atypical femoral fracture and the use of bisphosphonates. We should note that these atypical fractures occurred in

patients significantly younger than in patients with typical fractures.

The results of our study recommend a careful use of bisphosphonate, mainly beyond five years.

ACKNOWLEDGMENTS

The authors wish to acknowledge Joaquim G. Santos, an experienced Nuclear Medicine physician, for his support in the statistical analysis.

CONFLICT OF INTERESTS

The authors declare that there was no conflict of interests in writing this manuscript.

FINANCIAL SOURCES

The authors declare that there were no external financial sources for writing this manuscript.

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Acta Med Port 2014;27:704-709

Publicado pela **Acta Médica Portuguesa**, a Revista Científica da Ordem dos Médicos

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1749-084 Lisboa, Portugal.

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ISSN:0870-399X | e-ISSN: 1646-0758



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