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Oral bisphosphonates are associated with increased risk of subtrochanteric and diaphyseal fractures in elderly women: a nested case–control study

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ABSTRACT

Objectives: To evaluate the association between bisphosphonate use and the risk of atypical femoral fractures among women aged 65 or older.

Design: Nested case–control study.

Setting: General practice research database in Spain.

Exposures: Use of oral bisphosphonates before the occurrence of atypical fractures among cases or the corresponding index date among controls. Bisphosphonate use was categorised as ever versus never users. Ever users were divided according to the total time since first prescription.

Main outcome measures: Cases were defined as women aged 65 years or older with a first diagnosis of subtrochanteric or diaphyseal fracture, recorded in the BIFAP database between 1 January 2005 and 31 December 2008, and with at least 1 year of follow-up before the index date. For each case, five age-matched and calendar-year-matched controls without a history of hip or atypical fracture were randomly selected from the database.

Statistical analysis: OR of atypical femoral fracture by bisphosphonate use was determined using conditional logistic regression. Models were adjusted for comorbidities and use of other medications.

Results: The analysis included 44 cases and 220 matched controls (mean age, 82 years). Ever use of bisphosphonates was more frequent in cases than controls (29.6% vs 10.5%). In multivariate analyses, OR (95% CI) of atypical femoral fracture was 4.30 (1.55 to 11.9) in ever versus never users of bisphosphonates. The risk increased with long-term use, with an OR of 9.46 (2.17 to 41.3) comparing those using bisphosphonates over 3 years versus no users (p for trend=0.01).

Conclusions: Bisphosphonate use was associated with an increased risk of subtrochanteric or diaphyseal fractures in elderly women in a low fracture risk population, with a higher risk among long-term bisphosphonate users.

ARTICLE SUMMARY

Article focus

- The hypothesis of this study is that oral bisphosphonates may increase atypical femoral fracture risk in elderly women in long-term use.

Key messages

- Bisphosphonate use was associated with an increased risk of atypical femoral fractures in elderly women.
- A higher risk was observed among long-term bisphosphonate users.

Strengths and limitations of this study

- The main strength is that the observed ORs indicate a strong association between bisphosphonate use and increased atypical femoral fracture risk, which can hardly be challenged on grounds of bias in the design.
- One of the main limitations of this study is the small number of cases, which made it unfeasible to perform subgroup or individual drugs analyses. x-Ray images were not available. However, this may not be a relevant limitation; yet hip fracture cases are described in detail in the surgical procedures.

INTRODUCTION

Background

In 2005, Odvina *et al*[1] published the first paper warning about the potentially harmful effects of alendronate due to suppression of bone remodelling. Spontaneous fractures were observed in nine patients receiving long-term treatment with the drug (between 3 and 8 years). It was hypothesised that bisphosphonate long-term use might increase the risk of fracture and cause difficulties in repairing fractures in some patients.

Then more cases and short series of cases were described.[2–11] During 2009, a case–control study was carried out to evaluate the association between low impact femur fractures and the long-term use of bisphosphonates.[12] A comparison was made between 41 subtrochanteric or diaphyseal fractures with 82 control patients with femoral or

intertrochanteric fractures. A strong association was found between the use of bisphosphonates and atypical fractures. At the same time, a typical radiological pattern was described for the fractures related to bisphosphonates. During the same year, more cases and series of cases of femur fractures associated with the use of bisphosphonates were published.[13–16] The capacity of bisphosphonates to weaken bone structure is reflected in an article that describes a series of seven cases of bilateral fractures or sequential cases of low-impact fractures, all associated with the treatment with alendronate for at least 5 years.[17] These included one patient with simultaneous bilateral femur fractures affecting the diaphysis, two patients with sequential subtrochanteric fractures and four patients in whom a contralateral subtrochanteric fracture was discovered after diagnosing the initial fracture.

Finally, in two cohort analyses, bisphosphonate use was associated with a much higher relative risk of atypical fractures[18 19] (17-fold and 47-fold higher, respectively), while a recent case–control study showed a threefold increase in bisphosphonate users.[20] More studies in different populations with sufficient sample sizes are needed in order to shed more light on the use of bisphosphonates and atypical fracture risk.

Objective

The aim of this study is to evaluate the association between the use of bisphosphonates and the risk of subtrochanteric or diaphyseal fractures among women aged 65 years or older in a Mediterranean population. We hypothesised that oral bisphosphonates could increase subtrochanteric or diaphyseal fracture risk.

METHODS

Study design and setting

We carried out a case-control study nested in the Spanish database BIFAP (*Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria*, Database for Pharmacoepidemiological Research in Primary Care). This is a longitudinal population-based database maintained by the Spanish Agency for Medicines and Medical Devices that collects, from 2001 onwards, the computerised medical records of >3.2 million patients attended to by more than 1800 primary care physicians throughout Spain. It includes anonymised information on >13.7 million person-years of follow-up.[21 22] This project was approved by the Navarre Research Ethics Board, Pamplona, Spain.

Participants

Cases were defined as women aged 65 years or older with a first diagnosis of subtrochanteric or diaphyseal fracture, recorded between 1 January 2005 and 31 December 2008, and with at least 1 year of follow-up in BIFAP before the event date. Preselected cases for hip fracture were identified by both ICPC-2 codes and free text searching. All clinical records of the potential cases were manually reviewed by the BIFAP team blinded to the exposure status. The date of hospitalisation served as the index date. We excluded women with any history of cancer, Paget disease, prevalent hip fracture and fractures resulting from trauma or motor vehicle collisions. For each case, five controls with no history of hip fracture at the time of the index date of their corresponding case were selected, matched by the same age and calendar year of enrolment in BIFAP.

Medication use and other covariates

The use of bisphosphonates before the index date was obtained from the computerised database. Duration of bisphosphonate exposure was evaluated by examining prescriptions for oral alendronate, risedronate, ibandronate or etidronate from the beginning of therapy to the index date or the corresponding date among controls (ATC codes: alendronate, M05BA04; alendronate plus vitamin D, M05BB; risedronate, M05BA07 and ibandronate, M05BA06).

Individuals were classified as ever versus never users. Ever users were those with at least one prescription, with no minimum duration. Ever users were also divided into *current users* (if the most recent prescription lasted through the index date or ended in the month before it), *recent users* (if the most recent prescription ended between 1 and 6 months before the index date) and *past users* (if the most recent prescription ended more than 6 months before the index date).

In order to assess the effects of treatment length on the outcomes, four different subgroups were considered based on the cumulative duration of actual treatment, namely 30 days or less; >30 days to ≤1 year; >1 to ≤3 years and over 3 years. The effects of time of bisphosphonate exposure on atypical hip fracture risk were also analysed. Exposure was measured as the time (in days) since the first prescription.

Information on comorbilities (ICPC-2 codes) and the use of other medications (ATC codes) was obtained. The cumulative total days of treatment was calculated for each individual drug. The time between last prescription and index date was also calculated. Other variables such as weight (kg), height (cm), body mass index (kg/m^2) and smoking status (yes/no/past smoker) were obtained as well.

Statistical methods

We used conditional logistic regression to estimate the ORs and 95% CIs for the association between bisphosphonate exposure (ever vs never) and hip fractures. Treatment duration was assessed as well and results were tested to identify a trend. Tests for trend were performed assigning the median to each category of ordinal variables and including that value as a continuous variable in the models.The level of significance was established at p=0.05.

An initial model was adjusted only for matching variables. Additionally, a second model was adjusted for

smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, thyroid disease and use of proton pump inhibitors (no use, ≤1 year, >1 year), anxiolytics, sedatives, antidepressants, antihypertensives, corticosteroids (no use, ≤1 year, >1 year), raloxifene, hormone replacement therapy and thiazolidinediones.

RESULTS

Between 2005 and 2008, 45 atypical fractures (31 subtrochanteric and 14 shaft fractures) were observed. The average age of cases was 82.2±6.7 years. Previous fractures and drug use were more prevalent in cases than in controls (table 1).

Ever use of bisphosphonates was more frequent in cases than in controls, 13 (29.6%) versus 23 (10.5%) yielding to an adjusted OR=4.30 (95% CI 1.55 to 11.9). Within ever users, no apparent difference was observed between current, recent or past users, although the numbers were quite small. A duration-dependent association was suggested, with a higher risk among those with longer exposure to bisphosphonates (>3 years, OR=9.46 (95% CI 2.17 to 41.3) (table 2). The results by individual drugs are not shown because of insufficient sample size.

Table 1 Characteristics of cases and controls

	Cases	Controls
N	44	220
Age (years) (±SD)	82.2 (6.7)	82.2 (6.6)
Smoking (%)		
Non-current smoker	77.3	70.9
Current smoker	2.3	3.2
Not recorded	20.5	25.9
Alcoholism	0.0	0.0
Body mass index (kg/m^2) (±SD)	29.4 (4.9)	29.1 (5.3)
<20 kg/m^2 (%)	0.0	1.4
20–<25 kg/m^2 (%)	9.1	14.1
25–<30 kg/m^2 (%)	29.6	25.0
>=30 kg/m^2 (%)	31.8	32.3
Not recorded (%)	29.6	27.1
Comorbidities (%)		
Previous fracture	20.5	8.2
Kidney disease	4.6	5.0
Malabsorption	2.3	1.4
Stroke	9.1	6.4
Dementia	9.1	8.6
Rheumatoid arthritis	2.3	1.4
Diabetes	18.2	20.5
Epilepsy	2.3	0.5
Parkinson disease	0.0	1.8
Thyroid disease	9.1	13.2
Use of medication (%)		
PPI or H2 receptor blocker	34.1	33.2
Anxiolytic	22.7	24.1
Antidepressants	9.1	19.6
Antihypertensives	50.0	60.9
Oral corticosteroids	4.6	7.3
Sedatives	9.1	6.8
Raloxifene	0.0	2.3
Hormone replacement therapy	0.0	0.0
Thiazolidinedione	0.0	0.0

Values correspond to percentage or means (SD).

DISCUSSION

Key results

Our findings show an increase of atypical fracture risk among ever users of bisphosphonates versus never users, and a distinct duration–response association, with higher risk among women using bisphosphonates for a longer time period. Results did not vary for bisphosphonate use timing (current use, recent use and past use). Since these drugs accumulate in the bone and remain there for years, this grading system may not make any relevant difference, being more important than overall cumulative exposure expressed as time in days since the first prescription. Both unadjusted and adjusted data show a duration-dependent association between bisphosfonate use and higher risk of atypical fractures.

Both cohort and case-control studies show an increased risk of atypical fractures associated with bisphosphonate use. One peculiarity about our study is that it was carried out in a Mediterranean population, which has a lower risk of bone fractures compared to Anglo-Saxon or Northern European countries. It could be hypothesised that, because of the lower risk of fractures in the Spanish population, the association between bisphosphonates and subtrochanteric or diaphyseal fractures might not be evident. However, our results are similar to those obtained in the largest case-control study published so far[20] and show an overall fourfold higher risk. In this study, an association between long-term use and higher risk was also observed. In two cohort studies, the overall fracture risk observed was much higher.[18 19] A recent study also found a higher atypical femoral fracture risk associated with bisphosphonate use when classic fractures are used as controls. In this study, longer duration of treatment resulted in augmented risk.[23] Another cohort study with a follow-up period of 10 years also found that the incidence of atypical fractures increases with a longer duration of bisphosphonate use.[24]

Bisphosphonates induce apoptosis of the osteoclasts and inhibit bone resorption. However, during the normal process of bone remodelling, the formation of bone produced by osteoblasts is induced by osteoclasts, which implies that on reducing the resorptive activity, there is also an accompanying reduction in bone formation. The greater bone density observed after treatment with bisphosphonates may thus reflect bone weakness and not strength, given the increase of mineral content in the bone. Bisphosphonates also weaken the collagen structure and produce an accumulation of microscopic injuries in the bone structure. Biologically, this makes it

Table 2 Association of any bisphosphonate use with the risk of atypical femoral fracture

	Cases	Controls	Average cumulative duration (days)	Time since first bisphosphonate prescription (days)	Model 1	Model 2
	n (%)	n (%)	Mean (SD)	Mean (SD)	OR (95% CI)	OR (95% CI)
Use						
No use	31 (70.5)	197 (89.5)	–	–	1 (ref.)	1 (ref.)
Ever use	13 (29.6)	23 (10.5)	658 (538)	1007 (708)	3.63 (1.64 to 8.02)	4.30 (1.55 to 11.9)
Timing						
No use	31 (70.5)	197 (89.5)	–	–	1 (ref.)	1 (ref.)
Past use	3 (6.8)	6 (2.7)	567 (569)	1655 (772)	3.16 (0.76 to 13.0)	4.43 (0.62 to 31.9)
Recent use	1 (2.3)	2 (0.9)	299 (199)	448 (87)	4.89 (0.27 to 87.1)	3.40 (0.03 to 384)
Current use	9 (20.5)	15 (6.8)	737 (546)	835 (566)	3.76 (1.51 to 9.36)	4.29 (1.39 to 13.3)
Duration						
No use	31 (70.5)	197 (89.6)	–	–	1 (ref.)	1 (ref.)
≤1 year	4 (9.1)	8 (3.6)	156 (100)	675 (731)	3.27 (0.92 to 11.7)	2.55 (0.47 to 13.7)
>1–≤3 year	4 (9.1)	12 (5.5)	622 (213)	967 (673)	2.01 (0.58 to 6.92)	1.68 (0.36 to 7.85)
>3 year	5 (11.4)	3 (1.4)	1485 (341)	1587 (346)	9.18 (2.12 to 38.9)	31.9 (4.05 to 251)
p for trend*					0.002	0.0007
Time since first bisphosphonate prescription						
No use	31 (70.5)	197 (89.6)	–	–	1 (ref.)	1 (ref.)
<1 year	3 (6.8)	2 (0.9)	142 (120)	150 (130)	10.0 (1.6 to 62.0)	4.98 (0.56 to 44.2)
1–<3 year	4 (9.1)	13 (5.9)	446 (230)	659 (180)	1.94 (0.56 to 6.76)	1.72 (0.36 to 8.34)
≥3 year	6 (13.6)	8 (3.6)	1100 (582)	1737 (540)	4.71 (1.52 to 14.6)	9.46 (2.17 to 41.3)
p for trend†					0.03	0.01

Model 1: Conditional logistic regression model adjusted for matching variables.
Model 2: Conditional logistic regression model adjusted for matching variables, smoking, alcoholism, BMI, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, thyroid disease, PPI (no use, ≤1 year, >1 year), anxiolytics, sedatives, antidepressants, antihypertensives, corticosteroids (no use, ≤1 year, >1year), raloxifene, hormone replacement therapy and thiazolidinediones.
*Modelled as the median duration of use in each category.
†Modelled as time in days since first bisphosphonate prescription (0 for no users).
BMI, body mass index; PPI, proton pump inhibitor.

plausible that long-term bisphosphonate use would increase the risk of fracture and cause difficulty in repairing fractures.

Deleterious effects on bone structure have been observed with both bisphosphonates and denosumab but not with other drugs used for osteoporosis. Both types of drugs inhibit the activity of osteoclasts and, thereby, bone resorption. Since osteoblastic bone formation follows osteoclastic resorption during normal bone remodelling, the inhibition of resorption is accompanied by a decrease in bone formation. In other words, bone strength may be weaker as normal turnover is inhibited. Furthermore bisphosphonates prolong secondary mineralisation leading to increased bone mineral density (BMD) but decreased bone strength due to a higher mineral content (brittle bones).

A typical radiological pattern was described for the fractures related to bisphosphonates and a high association between the use of bisphosphonates and the appearance of this radiological pattern.[25] Also, Koh *et al*[26] determined that atypical lesions are more frequent in the femur regions of maximal tension loading. Thereby, there is a biological, radiological and mechanical rationale for an increase in atypical fracture risk associated with the use of bisphosphonates.

Limitations

One of the main limitations of this study is the small number of cases, which made it unfeasible to perform subgroup or individual drugs analyses and led to wide CIs in the estimates of association. Also, we relied on prescription data to determine the exposure status and duration of bisphosphonate exposure. It is sensible to think that real exposure will surely be lower than registered to some extent. However, this will most probably represent a non-differential misclassification that would distort the result towards the null value. Therefore, given that our findings show an increase in atypical fracture risk associated with bisphosphonate use, we may assume that it represents a conservative estimate.

BMD determination is not a standard test available in the public health system in Spain. Thereby, information on bone density in clinical records was rather scarce. In any case, this test has a very poor fracture risk predictive value and its clinical relevance can be challenged. In the present analysis, we adjusted for other bone-related variables. One of these, the prevalence of previous fractures, might confound the association between bisphosphonate use and the risk of fracture. In order to minimise confounding by indication bias, results were adjusted for previous fractures, comorbidities and use of other medications.

Finally, our study had a case-control design and not a cohort design, which is supposed to be a stronger method. However, our cases and controls were selected from a well-defined cohort, reducing the possibility of selection bias, and information on treatment use and comorbidities was recorded before hip fractures occurred, making differential misclassification of the exposure less likely.

CONCLUSION

Bisphosphonate use was associated with an increased risk of subtrochanteric or diaphyseal fractures in elderly women in a low fracture risk population, with a higher risk among long-term bisphosphonate users.

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Contributors JE, AA, JG, AL, JT, MG and FD were responsible for development of the study concept and design and interpretation of the results. JE, AA, JG, AL, JT and MG carried out the data validation. AA performed the statistical analyses. BO and CH were responsible for data extraction. JE drafted the manuscript. All authors have been involved in revising and elaborating it critically in the intellectual context.

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REFERENCES

1. Odvina CV, Zerwekh JE, Rao DS, *et al*. Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab* 2005;90:1294–301.
2. Schneider JP. Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. *Geriatrics* 2006;61:31–3.
3. Cheung R, Leung KK, Lee KC, *et al*. Sequential non-traumatic femoral shaft fractures in a patient on long-term alendronate. *Hong Kong Med J* 2007;13:485–9.
4. Lee P, van der Wall H, Seibel MJ. Looking beyond low bone mineral density: multiple insufficiency fractures in a woman with post-menopausal osteoporosis on alendronate therapy. *J Endocrinol Invest* 2007;30:590–7.
5. Goh SK, Yang KY, Koh JSB, *et al*. Subtrochanteric insufficiency fractures in patients on alendronate therapy. A caution. *J Bone Joint Surg Br* 2007;89-B:349–53.
6. Sayed-Noor AS, Sjödén GO. Suctrochanteric displaced insufficiency fracture after long-term alendronate therapy—a case report. *Acta Orthop* 2008;79:565–7.
7. Visekruna M, Wilson D, McKiernan FE. Severely suppressed bone turnover and atypical skeletal fragility. *J Clin Endocrinol Metabol* 2008;93:2948–52.
8. Kwek EBK, Koh JSB, Howe TS. More on atypical fractures of the femoral diaphysis (letter). *N Engl J Med* 2008;359:316–18.
9. Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate (letter). *N Engl J Med* 2008;358:1304–6.
10. Kwek EBK, Goh SK, Koh JSB,, *et al*. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? *Injury* 2008;39:224–31.
11. Neviaser AS, Lane JM, Lenart BA, *et al*. Low-energy femoral shaft fractures associated with alendronate use. *J Orthop Trauma* 2008;22:346–50.

12. Lenart BA, Neviaser AS, Lyman S, *et al*. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. *Osteoporos Int* 2009;20:1353–62.
13. Sabed-Noor AS, Sjödén GO. Two femoral insufficiency fractures after long-term alendronate therapy. *Clin Orthop Relat Res* 2009;467:1921–6.
14. Ing-Lorenzini K, Desmeules J, Plachta O, *et al*. Low-energy femoral fractures associated with the long-term use of bisphosphonates. A case series from a Swiss University Hospital. *Drug Saf* 2009;32:775–85.
15. Goddard MS, Kristoff RR, Johnston JC, *et al*. A traumatic bilateral femur fracture in long-term bisphosphonate use. *Orthopedics* 2009;32:607.
16. Odvina CV, Levy S, Rao S, *et al*. Unusual mid-shaft fractures during long term bisphosphonate therapy. *Clin Endocrinol (Oxf)*. 2010;72:161–8.
17. Capeci CM, Tejwani NC. Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. *J Bone Joint Surg Am* 2009;91:2556–61.
18. Giusti A, Hamdy NA, Dekkers OM, *et al*. Atypical fractures and bisphosphonate therapy: a cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features. *Bone* 2011;48:966–71.
19. Schilcher J, Michaëlsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med* 2011;364:1728–37.
20. Park-Wyllie LY, Mamdani MM, Juurlink DN, *et al*. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. *JAMA* 2011;305:783–9.
21. Salvador Rosa JC, Moreno Pérez D, *et al*. El Proyecto BIFAP: Base de datos para la Investigación. *Aten Primaria* 2002;30:655–61.
22. Agencia Española de Medicamentos y Productos Sanitarios. Proyecto BIFAP http://www.bifap.org/summary.php (accessed 4 Sept 2012).
23. Meier RPH, Perneger TV, Stern R, *et al*. Increasing occurrence od atypical femoral fractures associated with bisphosphonate use. *Arch Intern Med* 2012;172:930–6.
24. Dell RM, Adams AL, Greene DF, *et al*. Incidence of Atypical Nontraumatic Diaphyseal Fractures of the Femur. *JBMR* 2012;27:2544–50.
25. Lenart BA, Neviaser AS, Lyman S, *et al*. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. *Osteoporos Int* 2009;20:1353–62.
26. Koh JSB, Goh SK, Png MA, *et al*. Distribution of atypical fractures and cortical stress lesions in the femur: implications on pathophysiology. *Singapore Med J* 2011;52:77–80.