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TITLE

ORAL BISPHOSPHONATES ARE ASSOCIATED WITH INCREASED RISK OF ATYPICAL FEMORAL FRACTURES IN ELDERLY WOMEN

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ARTICLE SUMMARY

Article Focus

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

Key messages

. Bisphosphonate use was associated with an increased risk of atypical femoral fractures in elderly women

. A higher risk among long-term bisphosphonate users was observed.

Strengths and limitations

. The main strength is that the observed odds ratios indicate a strong association between bisphosphonate use and increased atypical femoral fracture risk that 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.

ABSTRACT

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

Design:
Nested case-control study

Setting:
General practice research database in Spain.

Participants:
Cases were defined as women aged 65 years or older with a first diagnosis of atypical femoral fracture (subtrochanteric or diaphyseal). For each case, 5 age- and calendar year-matched controls without history of hip or atypical fracture were randomly selected.

Interventions:
Information on bisphosphonate use, atypical femoral fractures, comedication, and comorbidities was collected.

Primary outcomes
Atypical femoral fracture risk comparing bisphosphonate users vs never users

Secondary outcomes
Atypical femoral fracture risk comparing bisphosphonate users vs never users by individual drugs

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 (1.55-11.9) in ever vs never users of bisphosphonates. A duration-dependent association was suggested, with higher risk among those with longer exposure to bisphosphonates regardless the criteria used, either cumulative duration (>3 years, OR=31.9; 95%CI, 4.05-251) or time since first prescription (>3 years, OR=9.46; 95%CI, 2.17-41.3), p for trend=0.01.

Conclusions:
Bisphosphonate use was associated with an increased risk of atypical femoral fractures in elderly women, with a higher risk among long-term bisphosphonate users.

Trial Registration
Spanish Ministry of Health. TRA-071

INTRODUCTION

Background

In 2005, *Odvina* et al published the first paper warning about the potentially harmful effects of alendronate due to suppression of bone remodelling.[1] Spontaneous fractures were observed in 9 patients receiving long-term treatment with the drug (between 3-8 years). It was hypothesized 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 inter-trochanteric 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 five 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 and 47-fold higher, respectively) while a recent case-control study showed a 3-fold increase in bisphosphonate users.[20] More studies in different populations with sufficient sample size 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 use of bisphosphonates and risk of atypical femoral fractures among women aged 65 years or older in a Mediterranean population. We hypothesized that oral bisphosphonates could increase atypical 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 Pharmacoepidemiologic 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 computerized medical records of >3.2 million patients attended by more than 1,800 primary care physicians throughout Spain. It includes anonymized information on >13.7 million person-years of follow up.[21,22] This project was approved by the Navarre Research Ethics Board, Pamplona, Spain. All data were anonymized and no written consent was necessary for this type of study according to the Spanish regulations (law 41/2002, article 16).

Participants

Cases were defined as women aged 65 years or older with a first diagnosis of atypical femoral fracture (subtrochanteric or diaphyseal), recorded between 01/01/2005 and 31/12/2008, and with at least 1 year of follow-up in BIFAP before the event date. Pre-selected cases for hip fracture were identified by both ICPC-1 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 hospitalization served as the index date. We studied in detail the description of the atypical fractures in the clinical records and made sure about the location (subtrochanteric region and femoral shaft). We excluded women with any history of

cancer, Paget disease, prevalent hip fracture and fractures resulting from trauma or motor vehicle collisions. All cases were double-checked by the Spanish Medicines Agency experts. For each case, 5 age- and calendar year-matched controls without history of hip or atypical fracture were randomly selected from the database.

Medication use and other covariates

Use of bisphosphonates before the index date was obtained from the computerized 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 vs never users. Ever users were also divided into *current users* (if most recent prescription lasted through index date or ended in the month before it), *recent users* (if most recent prescription ended between 1 and 6 months before index date) and *past users* (if most recent prescription ended more than 6 months before index date).

In order to assess the effects of treatment length on the outcomes two criteria were used: a) Cumulative duration of actual treatment; and b) Time since first prescription. In both, three different subgroups were considered, namely <1 year; 1 to 3 years and over 3 years.

Information on comorbilities (ICPC-1 codes) and use of other medications (ATC codes) was obtained. Patients were considered exposed if the most recent prescription lasted through index date or ended in the month before it. 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 odds ratios (ORs) and 95 percent confidence intervals (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. The level of significance was established at p = 0.05.

An initial model adjusted only for matching variables. A second model adjusted additionally for smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, thyroid disease, and use of PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones.

RESULTS

Between 2005 and 2008, 45 atypical fractures (31 subtrochanteric and 14 shaft fractures) were observed. One case was lost to follow-up due to lack of matching

controls. The average age of cases was 82.2 ± 6.7 years. Previous fractures and drug use was more prevalent in cases than in controls (table 1).

Ever use of bisphosphonates was more frequent in cases than in controls, 13 (29.6%) vs 23 (10.5%) yielding to an adjusted OR = 4.30 (95%CI, 1.55-11.9). Within ever users no apparent difference was observed between current, recent or past users, although numbers were quite small. A duration-dependent association was suggested, with higher risk among those with longer exposure to bisphosphonates regardless the criteria used, either cumulative duration (>3 years, OR=31.9; 95%CI, 4.05-251) or time since first prescription (>3 years, OR=9.46; 95%CI, 2.17-41.3) (table 2). The results by individual drugs are not shown because of insufficient sample size.

DISCUSSION

Key results

Our findings show an increase of atypical fracture risk among *ever users* of bisphosphonates vs *never users*, and a distinct duration-response association, with higher risk among women using bisphosphonates for longer time period. Results did not vary for bisphosphonate use timing (current use, recent use, 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 the overall cumulative exposure expresed 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 regardless the criteria used, either cumulative duration or time since first prescription.

Both cohort and case-control studies show an increased risk of atypical fractures associated with bisphosphonate use. Our results are similar to those obtained in the largest case-control study published so far[20] and show an overall 4-fold higher risk. In this study an association between long-term use and higher risk was also observed. In two cohort studies overall fracture risk observed was much higher.[18,19]

Bisphosphonates induce apoptosis of the osteoclasts and inhibit bone resorption. However, during the normal process of bone remodeling 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 bone structure. Biologically, this makes it 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 type 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 mineralization leading to increased 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.[23] Also Koh et al determined that atypical lesions are more frequent in femur regions of maximal tension loading.[24] Thereby there is 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. Also we relied on prescription data to determine exposure status and duration of bisphosphonate exposure. It is sensible to think that real exposure will likely 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. In the clinical records included in the BIFAP database X-ray images are not available which might occasionally lead to misclassification of cases. However we believe this may not be a relevant limitation yet hip fracture cases are described in detail in the surgical procedures.

Bone mineral density 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 prevalence of previous fractures might confound the association between bisphosphonate use and risk of fracture. In order to minimize confounding by indication bias, results were adjusted for previous fractures, comorbidities and use of other medications.

CONCLUSION

Bisphosphonate use was associated with an increased risk of atypical femoral fractures in elderly women in a Mediterranean population, with a higher risk among long-term bisphosphonate users.

Acknowledgements

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Disclaimer:

The views expressed are those of the authors only and do not represent necessarily the position of their respective institutions.

Footnotes

- Contributors JE, AA, JG, AL, JT, MG, and FD were responsible for developing of 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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- Competing interests: None.
- Ethics approval: Navarre Research Ethics Board, Pamplona, Spain.
- Data sharing statement: There are no additional data sharing to other parties.

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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 (standard deviation)

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 (1.64-8.02)	4.30 (1.55-11.9)
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 (0.76-13.0)	4.43 (0.62-31.9)
Recent use	1 (2.3)	2 (0.9)	299 (199)	448 (87)	4.89 (0.27-87.1)	3.40 (0.03-384)
Current use	9 (20.5)	15 (6.8)	737 (546)	835 (566)	3.76 (1.51-9.36)	4.29 (1.39-13.3)
Duration						
No use	31 (70.5)	197 (89.6)	-	-	1 (ref.)	1 (ref.)
≤1 yr	4 (9.1)	8 (3.6)	156 (100)	675 (731)	3.27 (0.92-11.7)	2.55 (0.47-13.7)
>1 yr - ≤3 yr	4(9.1)	12 (5.5)	622 (213)	967 (673)	2.01 (0.58-6.92)	1.68 (0.36-7.85)
>3 yr	5 (11.4)	3 (1.4)	1485 (341)	1587 (346)	9.18 (2.12-38.9)	31.9 (4.05-251)
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 yr	3 (6.8)	2 (0.9)	142 (120)	150 (130)	10.0 (1.6-62.0)	4.98 (0.56-44.2)
1 - <3yr	4 (9.1)	13 (5.9)	446 (230)	659 (180)	1.94 (0.56-6.76)	1.72 (0.36-8.34)
≥3 yr	6 (13.6)	8 (3.6)	1100 (582)	1737 (540)	4.71 (1.52-14.6)	9.46 (2.17-41.3)
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 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones.

* Modeled as the median duration of use in each category; ** Modeled as time in days since first bisphosphonate prescription (0 for no users)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract. **OK**	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **OK**	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **OK**	
Objectives	3	State specific objectives, including any pre-specified hypotheses **OK**	
Methods			
Study design	4	Present key elements of study design early in the paper **OK**	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **OK**	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **OK** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case **OK**	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **OK**	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **OK**	
Bias	9	Describe any efforts to address potential sources of bias **OK**	
Study size	10	Explain how the study size was arrived at **OK**	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **OK**	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **OK**	
		(*b*) Describe any methods used to examine subgroups and interactions **OK**	
		(*c*) Explain how missing data were addressed **OK**	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed **OK**	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **OK**	
		(b) Give reasons for non-participation at each stage Not applicable	
		(c) Consider use of a flow diagram Not applicable	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **OK**	
		(b) Indicate number of participants with missing data for each variable of interest **OK**	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure **OK**	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **OK**	
		(*b*) Report category boundaries when continuous variables were categorized **OK**	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **OK**	
Discussion			
Key results	18	Summarise key results with reference to study objectives **OK**	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **OK**	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **OK**	
Generalisability	21	Discuss the generalisability (external validity) of the study results **OK**	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **OK**	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

ORAL BISPHOSPHONATES ARE ASSOCIATED WITH INCREASED RISK OF ATYPICAL FEMORAL FRACTURES IN ELDERLY WOMEN

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Keywords:	CLINICAL PHARMACOLOGY, EPIDEMIOLOGY, PRIMARY CARE

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 (standard deviation)

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 (1.64-8.02)	4.30 (1.55-11.9)
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 (0.76-13.0)	4.43 (0.62-31.9)
Recent use	1 (2.3)	2 (0.9)	299 (199)	448 (87)	4.89 (0.27-87.1)	3.40 (0.03-384)
Current use	9 (20.5)	15 (6.8)	737 (546)	835 (566)	3.76 (1.51-9.36)	4.29 (1.39-13.3)
Duration						
No use (≤30 d)	31 (70.5)	197 (89.6)	-	-	1 (ref.)	1 (ref.)
>30 d ≤1 yr	4 (9.1)	8 (3.6)	156 (100)	675 (731)	3.27 (0.92-11.7)	2.55 (0.47-13.7)
>1 yr - ≤3 yr	4(9.1)	12 (5.5)	622 (213)	967 (673)	2.01 (0.58-6.92)	1.68 (0.36-7.85)
>3 yr	5 (11.4)	3 (1.4)	1485 (341)	1587 (346)	9.18 (2.12-38.9)	31.9 (4.05-251)
P for trend					0.002	0.0007
Time since first bisphosphonate prescription						
No use (≤30 d)	31 (70.5)	197 (89.6)	-	-	1 (ref.)	1 (ref.)
>30 d ≤1 yr	3 (6.8)	2 (0.9)	142 (120)	150 (130)	10.0 (1.6-62.0)	4.98 (0.56-44.2)
>1 yr - ≤3 yr	4 (9.1)	13 (5.9)	446 (230)	659 (180)	1.94 (0.56-6.76)	1.72 (0.36-8.34)
>3 yr	6 (13.6)	8 (3.6)	1100 (582)	1737 (540)	4.71 (1.52-14.6)	9.46 (2.17-41.3)
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 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones.

* Modeled as the median duration of use in each category; ** Modeled as time in days since first bisphosphonate prescription (0 for no users)

TITLE

ORAL BISPHOSPHONATES ARE ASSOCIATED WITH INCREASED RISK OF ~~ATYPICAL FEMORAL~~SUBTROCHANTERIC AND DIAPHYSEAL FRACTURES IN ELDERLY WOMEN

Juan Erviti[1], Álvaro Alonso[2,3], Belén Oliva[4], Javier Gorricho[1], Antonio López[1], Julia Timoner[4], Consuelo Huerta[4], Miguel Gil[4] and Francisco De Abajo[4,5].

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ARTICLE SUMMARY

Article Focus

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

Key messages

. Bisphosphonate use was associated with an increased risk of atypical femoral fractures in elderly women

. A higher risk among long-term bisphosphonate users was observed.

Strengths and limitations

. The main strength is that the observed odds ratios indicate a strong association between bisphosphonate use and increased atypical femoral fracture risk that 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.

ABSTRACT

Background: Case reports and a few epidemiological studies have shown an increased risk of atypical femoral fractures associated with bisphosphonate use. The evidence is, however, scarce and more formal studies are needed.

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

Methods:
Design. Nested case-control study
Setting. The study was performed in a general practice research database in Spain.
Exposures. Use of oral bisphosphonates any time before the occurrence of atypical fractures among cases or the corresponding index date among controls. Bisphosphonate use was categorized as ever vs 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 atypical femoral fracture (subtrochanteric or diaphyseal), recorded in the BIFAP database between 01/01/2005 and 31/12/2008, and with at least one year of follow-up before the index date. All cases were validated. For each case, 5 age- and calendar year-matched controls without history of hip or atypical fracture were randomly selected from the database.
Statistical analysis. OR and 95%CI of atypical femoral fracture by bisphosphonate use were 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 (1.55-11.9) in ever vs never users of bisphosphonates. The risk increased with long-term use, with an OR of 9.46 (2.17-41.3) comparing those using bisphosphonates over 3 years vs no users (p for trend=0.01).

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

INTRODUCTION

Background

In 2005, *Odvina* et al published the first paper warning about the potentially harmful effects of alendronate due to suppression of bone remodelling.[1] Spontaneous fractures were observed in 9 patients receiving long-term treatment with the drug (between 3-8 years). It was hypothesized 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 inter-trochanteric 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 five 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 and 47-fold higher, respectively) while a recent case-control study showed a 3-fold increase in bisphosphonate users.[20] More studies in different populations with sufficient sample size 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 use of bisphosphonates and risk of subtrochanteric or diaphyseal ~~atypical femoral~~ fractures among women aged 65 years or older in a Mediterranean population. We hypothesized that oral bisphosphonates could increase subtrochanteric or diaphyseal ~~atypical~~ 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 Pharmacoepidemiologic 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 computerized medical records of >3.2 million patients attended by more than 1,800 primary care physicians throughout Spain. It includes anonymized 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 ~~atypical femoral fracture (~~subtrochanteric or diaphyseal~~)~~ fracture, recorded between 01/01/2005 and 31/12/2008, and with at least 1 year of follow-up in BIFAP before the event date. Pre-selected 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 hospitalization 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, 5 controls with no history of hip fracture at the time of the index date of their corresponding case were selected, matched by same age and calendar year of enrolment in BIFAP.

Medication use and other covariates

Use of bisphosphonates before the index date was obtained from the computerized 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 vs never users. Ever users were those with at least one prescription, with no minimum duration. Ever users were also divided into *current users* (if most recent prescription lasted through index date or ended in the month before it), *recent users* (if most recent prescription ended between 1 and 6 months before index date) and *past users* (if most recent prescription ended more than 6 months before index date).

In order to assess the effects of treatment length on the outcomes four different subgroups were considered based on 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 analyzed. Exposure was measured as the time (in days) since the first prescription.

Information on comorbilities (ICPC-2 codes) and use of other medications (ATC codes) was obtained. Cumulative total days of treatment was calculated for each individual drug. 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 odds ratios (ORs) and 95 percent confidence intervals (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 adjusted only for matching variables. A second model adjusted additionally for smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, thyroid disease, and use of PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, corticosteroids (no use, <=1 yr, >1 yr), 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 was more prevalent in cases than in controls (table 1).

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

DISCUSSION

Key results

Our findings show an increase of atypical fracture risk among *ever users* of bisphosphonates vs *never users*, and a distinct duration-response association, with higher risk among women using bisphosphonates for longer time period. Results did not vary for bisphosphonate use timing (current use, recent use, 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 the overall cumulative exposure expresed 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. Our results are similar to those obtained in the largest case-control study published so far[20] and show an overall 4-fold higher risk. In this study an association between long-term use and higher risk was also observed. In two cohort studies 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 longer duration of bisphosphonate use.[24]

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Bisphosphonates induce apoptosis of the osteoclasts and inhibit bone resorption. However, during the normal process of bone remodeling 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 bone structure. Biologically, this makes it 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 type 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 mineralization leading to

increased 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~~3~~] Also Koh et al determined that atypical lesions are more frequent in femur regions of maximal tension loading.[26~~4~~] Thereby there is 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 confidence intervals in the estimates of association.. Also we relied on prescription data to determine 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.

Bone mineral density 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 prevalence of previous fractures might confound the association between bisphosphonate use and risk of fracture. In order to minimize 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 ~~atypical femoral~~ fractures in elderly women in a ~~Mediterranean~~ low fracture risk population, with a higher risk among long-term bisphosphonate users.

Acknowledgements

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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 (standard deviation)

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 (1.64-8.02)	4.30 (1.55-11.9)
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 (0.76-13.0)	4.43 (0.62-31.9)
Recent use	1 (2.3)	2 (0.9)	299 (199)	448 (87)	4.89 (0.27-87.1)	3.40 (0.03-384)
Current use	9 (20.5)	15 (6.8)	737 (546)	835 (566)	3.76 (1.51-9.36)	4.29 (1.39-13.3)
Duration						
No use	31 (70.5)	197 (89.6)	-	-	1 (ref.)	1 (ref.)
≤1 yr	4 (9.1)	8 (3.6)	156 (100)	675 (731)	3.27 (0.92-11.7)	2.55 (0.47-13.7)
>1 yr - ≤3 yr	4(9.1)	12 (5.5)	622 (213)	967 (673)	2.01 (0.58-6.92)	1.68 (0.36-7.85)
>3 yr	5 (11.4)	3 (1.4)	1485 (341)	1587 (346)	9.18 (2.12-38.9)	31.9 (4.05-251)
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 yr	3 (6.8)	2 (0.9)	142 (120)	150 (130)	10.0 (1.6-62.0)	4.98 (0.56-44.2)
1 - <3yr	4 (9.1)	13 (5.9)	446 (230)	659 (180)	1.94 (0.56-6.76)	1.72 (0.36-8.34)
≥3 yr	6 (13.6)	8 (3.6)	1100 (582)	1737 (540)	4.71 (1.52-14.6)	9.46 (2.17-41.3)
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 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones.

* Modeled as the median duration of use in each category; ** Modeled as time in days since first bisphosphonate prescription (0 for no users)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract. **OK**	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **OK**	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **OK**	
Objectives	3	State specific objectives, including any pre-specified hypotheses **OK**	
Methods			
Study design	4	Present key elements of study design early in the paper **OK**	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **OK**	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **OK** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case **OK**	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **OK**	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **OK**	
Bias	9	Describe any efforts to address potential sources of bias **OK**	
Study size	10	Explain how the study size was arrived at **OK**	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **OK**	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **OK**	
		(*b*) Describe any methods used to examine subgroups and interactions **OK**	
		(*c*) Explain how missing data were addressed **OK**	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed **OK**	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **OK**	
		(b) Give reasons for non-participation at each stage Not applicable	
		(c) Consider use of a flow diagram Not applicable	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **OK**	
		(b) Indicate number of participants with missing data for each variable of interest **OK**	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure **OK**	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **OK**	
		(*b*) Report category boundaries when continuous variables were categorized **OK**	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **OK**	
Discussion			
Key results	18	Summarise key results with reference to study objectives **OK**	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **OK**	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **OK**	
Generalisability	21	Discuss the generalisability (external validity) of the study results **OK**	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **OK**	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Manuscript ID bmjopen-2012-002091 entitled "ORAL BISPHOSPHONATES ARE ASSOCIATED WITH INCREASED RISK OF ATYPICAL FEMORAL FRACTURES IN ELDERLY WOMEN"

Let us first express our gratitude to the reviewers for their relevant inputs to the manuscript. Their contribution clearly improved the quality of the draft. Please find below our response to the reviewers' comments (text in blue colour)

Reviewer: Donald Morrish MD
362 HMRC
University of Alberta
Edmonton, Alberta, Canada T6G2C8
Professor of Medicine, Division of Endocrinology and Metabolism No competing interests.

The literature is adequately quoted

The study is well done within the limitations stated by the authors. However there is a rather small sample size compared to the largest study reported, by Park-Wyllie et al (2011) which had 716 atypical fractures. I am not sure this study therefore adds anything new to the literature.

We agree the study published by Park-Wyllie et al (2011) has a much larger sample size. Apart from this study, there are just a few studies with a sample size around 40 cases. One peculiarity about our study is that it was carried out in a Mediterranean population, with a lower risk for bone fractures compared to Anglo-Saxon or Northern European countries (Kanis JA, et al. International variations in hip fracture probabilities: implications for risk assessment. JBMR 2002;17:1237-1244). It could be hypothesized 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 that was not the case and our findings support this association even in a low-risk population.

Because of rather small sample size, studies on atypical fractures bear a high risk of bias. Thereby it is important to replicate them in different populations and databases. BIFAP database is a non-profit research project operated by the Spanish Medicines Agency, a public agency belonging to the Spanish Department of Health. The Spanish Medicines Agency guarantees the quality of the database. The fact that our study presents outcomes consistent with the findings in other similar studies supports the association between the use of bisphosphonates and the incidence of subtrochanteric and diaphyseal fracture risk.

The study is well done, but the sample size is rather small. The study duplicates other small studies and reaches the same conclusion. Since the database contains over 3.2 million patients, could more atypical fractures be found? This would make the study much stronger. (The Park-Wyllie study had 716 atypical fractures)

Please find below the main differences between the Park-Wyllie study and ours that may explain the different number of cases found in each study:

Park-Wyllie study includes cases registered during 6 years (April 1st 2003 to March 31st 2009) whereas in our study this is a 4-year period instead (January 1st 2005 to December 31st 2008). The average follow-up period was 7 years in Park-Wyllie study and 2.75±1.94 years in our study.

Park-Wyllie study includes a cohort of some 800,000 women aged >68 years using bisphosphonates. Our study had a total population of 3.2 million patients but our

cohort of women aged >65 years included approximately 280,000 individuals. As well as being a larger cohort, Park-Wyllie included women at higher risk of fracture, eg previous fractures in 70% of patients in Park-Wyllie and 20% in our study (see Baseline Characteristics of Cases and Controls in each study).

Finally, Spanish populations have a lower risk of fracture compared with the Anglo-Saxon populations after adjusting for number of risk factors.

Reviewer: Lydia Gedmintas
Rheumatology clinical research fellow
Brigham and Women's Hospital
USA

This is a very timely topic of research.

At this point in the study of the association of bisphosphonates and atypical femur fracture, it is important to attempt to confirm radiographic confirmation of these fractures. If this is not possible with the dataset used, the authors should address this and consider changing the title of the study as the ASBMR has determined that atypical femur fracture definition requires radiographic confirmation. Therefore the title of this study should likely be "subtrochanteric and diaphyseal fractures" rather than "atypical femoral fractures" as the authors were not able to radiologically confirm the fractures. This is an important distinction as prior studies have shown significant misclassification of these fractures based on diagnostic coding alone.

We absolutely agree with this comment and the title will be changed according to the reviewer's suggestion.

In regards to the study design, many prior papers have addressed ever/never use of bisphosphonates and associations with atypical femur fracture. Duration of bisphosphonate and its association with atypical femur fracture is currently the area of interest in the literature-- the authors therefore appropriately address duration in their study design. However, it is unclear why there were two definitions of treatment length; it would be helpful if this was explained further or potentially only use "cumulative duration of actual treatment" as this is likely the definition of most interest.

We assessed duration of bisphosphonate use in two different ways. First, as the cumulative use of bisphosphonates since the first prescription and, second, as the time since the first prescription. The idea behind this choice was to capture two different aspects of bisphosphonate use: the total use and the total time that the bone has been exposed to bisphosphonates. As we explain in the manuscript discussion, pathophysiological reasons support both measures. Therefore, we prefer to report both. Nonetheless, the methods section clarifies the definitions of cumulative exposure, which now reads as follows:

> In order to assess the effects of treatment length on the outcomes four different subgroups were considered based on 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 analyzed. Exposure was measured as the time (in days) since the first prescription.

These changes were also included in table 2.

It would be helpful for the authors to go into further detail of how bisphosphonate use was defined - for example, was there a minimum exposure, such as 30 days, required before labeling the patient as a bisphophonate user?

A patient was categorized as bisphosphonate user if she had any prescription for bisphosphonates (no minimum duration was required), though a majority of users had prescriptions for more than 30 days (see table 2 in the manuscript). Oral bisphosphonate presentations in Spain provide medication for 28 days. We have clarified this issue in the methods section of the manuscript:

> Individuals were classified as ever vs never users. Ever users were those with at least one prescription, with no minimum duration.

Lastly, a cohort design is likely a stronger method to address duration of use, and this may be something that the authors could consider.

We agree with the reviewer that cohorts are in general a better study design than case-control studies, because they are less likely to suffer from recall bias, differential misclassification of exposure, and selection bias due to inappropriate selection of controls. However, our case-control study does not have those problems since cases and controls were nested in a well-defined dynamic cohort, removing the risk of selection bias, and information on treatments and comorbidities was collected before the outcome occurred, reducing the threat of differential misclassification of the exposure. In fact, conducting a case-control study instead of a cohort study is a more efficient use of resources since the same results are obtained with a much smaller sample size. Duration of use was defined in the same way that it would have been defined in a cohort study, that is, the time using bisphosphonate before having a hip fracture before a woman had the event, or the equivalent time for a woman without a fracture. We have added a short paragraph to the discussion highlighting this issue:

> 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.

In regards to the statistical methods, it was unclear what methods were used particularly when performing trend and this could be more clearly discussed. In addition, while all the covariates used in the multivariable model are important and associated with fracture, considering the number of covariates and the small sample size this could lead to overadjustment.

Linear trends were calculated assigning the median value to each category, and including that value as a continuous variable in all models. This approach takes into account the distribution of the variable within each category and prevents outliers having a large impact in our estimates. This has been clarified in the methods section:

> 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.

Regarding the multivariable adjustment, we decided to adjust for all possible confounders in spite of the limited sample size to avoid residual confounding in the estimates as much as possible. Notably, results from model 1 (minimally adjusted) and model 2 (multivariable) were qualitatively similar, showing increased risk of atypical fractures with increased duration use. Therefore, 'overadjustment' is unlikely to be responsible for our study results. Nonetheless, we recognize this is a limitation, leading to imprecise estimates with wide confidence intervals, and the revised version states it clearly. We have included the following sentence in the discussion:

> 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 confidence intervals in the estimates of association.

Would benefit from editing prior to publication for ease of reading.

OK.

Two recent papers, Meier RP et al, Arch Int Med, 2012 and Dell RM, JBMR, 2012 are important recent contributions to this field using radiographic confirmation of atypical femur fracture, and should likely be discussed in the setting of this study. It would be helpful if the authors addressed what niche their study fills in the current literature of atypical femur fracture.

OK. Thank you for the contribution. The main niche of this study is the effects of bisphosphonates in a low fracture risk population. Please see the tracked new version of the manuscript

While the main research question addressed, ie the association of ever use of bisphosphonates and atypical femur fractures, is clear from the conclusions, the conclusions made from the results with duration of use are less clear. The multivariate analysis with this small number of cases may not be the most accurate way to present the data, as it is unclear if this data is overadjusted. In addition, it is unclear if a strong conclusion can be made from this trend test using these small number of cases.

We agree with the reviewer that the reduced number of cases limits the ability to make strong inferences for these results. This uncertainty is reflected by the wide confidence intervals in our estimates of association for the duration of use analyses. However, there are two reasons why we think these results are valuable. First, the trend analysis, which is more powerful to detect linear associations than the categorical analysis, showed highly significant associations between duration of use and risk of atypical fracture. Second, results from model 1 (minimally adjusted) and model 2 (multivariable) were qualitatively quite similar, i.e. both showed higher risk of fracture with increased duration of use. Differences in the magnitude of the association between models 1 and 2 are most likely due to the limited number of cases and, therefore, should be evaluated with caution. We believe that presenting multivariable adjusted models is necessary to demonstrate that confounding is not the main reason responsible for this association. To highlight the uncertainty of our results, though, we have including the following sentences in the discussion:

> 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 confidence intervals in the estimates of association.

It would be helpful in the conclusion to discuss some of the more recent studies suggested above that have addressed the issue of duration and discuss this paper in their context.

OK. Please see the tracked new version of the manuscript.

ORAL BISPHOSPHONATES ARE ASSOCIATED WITH INCREASED RISK OF ATYPICAL FEMORAL FRACTURES IN ELDERLY WOMEN

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Keywords:	CLINICAL PHARMACOLOGY, EPIDEMIOLOGY, PRIMARY CARE

TITLE

ORAL BISPHOSPHONATES ARE ASSOCIATED WITH INCREASED RISK OF SUBTROCHANTERIC AND DIAPHYSEAL FRACTURES IN ELDERLY WOMEN

Juan Erviti[1], Álvaro Alonso[2,3], Belén Oliva[4], Javier Gorricho[1], Antonio López[1], Julia Timoner[4], Consuelo Huerta[4], Miguel Gil[4] and Francisco De Abajo[4,5].

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ARTICLE SUMMARY

Article Focus

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

Key messages

. Bisphosphonate use was associated with an increased risk of atypical femoral fractures in elderly women

. A higher risk among long-term bisphosphonate users was observed.

Strengths and limitations

. The main strength is that the observed odds ratios indicate a strong association between bisphosphonate use and increased atypical femoral fracture risk that 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.

ABSTRACT

Background: Case reports and a few epidemiological studies have shown an increased risk of atypical femoral fractures associated with bisphosphonate use. The evidence is, however, scarce and more formal studies are needed.

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

Methods:
Design. Nested case-control study
Setting. The study was performed in a general practice research database in Spain.
Exposures. Use of oral bisphosphonates any time before the occurrence of atypical fractures among cases or the corresponding index date among controls. Bisphosphonate use was categorized as ever vs 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 atypical femoral fracture (subtrochanteric or diaphyseal), recorded in the BIFAP database between 01/01/2005 and 31/12/2008, and with at least one year of follow-up before the index date. All cases were validated. For each case, 5 age- and calendar year-matched controls without history of hip or atypical fracture were randomly selected from the database.
Statistical analysis. OR and 95%CI of atypical femoral fracture by bisphosphonate use were 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 (1.55-11.9) in ever vs never users of bisphosphonates. The risk increased with long-term use, with an OR of 9.46 (2.17-41.3) comparing those using bisphosphonates over 3 years vs 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.

INTRODUCTION

Background

In 2005, *Odvina* et al published the first paper warning about the potentially harmful effects of alendronate due to suppression of bone remodelling.[1] Spontaneous fractures were observed in 9 patients receiving long-term treatment with the drug (between 3-8 years). It was hypothesized 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 inter-trochanteric 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 five 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 and 47-fold higher, respectively) while a recent case-control study showed a 3-fold increase in bisphosphonate users.[20] More studies in different populations with sufficient sample size 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 use of bisphosphonates and risk of subtrochanteric or diaphyseal fractures among women aged 65 years or older in a Mediterranean population. We hypothesized 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 Pharmacoepidemiologic 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 computerized medical records of >3.2 million patients attended by more than 1,800 primary care physicians throughout Spain. It includes anonymized 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 01/01/2005 and 31/12/2008, and with at least 1 year of follow-up in BIFAP before the event date. Pre-selected 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 hospitalization 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, 5 controls with no history of hip fracture at the time of the index date of their corresponding case were selected, matched by same age and calendar year of enrolment in BIFAP.

Medication use and other covariates

Use of bisphosphonates before the index date was obtained from the computerized 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 vs never users. Ever users were those with at least one prescription, with no minimum duration. Ever users were also divided into *current users* (if most recent prescription lasted through index date or ended in the month before it), *recent users* (if most recent prescription ended between 1 and 6 months before index date) and *past users* (if most recent prescription ended more than 6 months before index date).

In order to assess the effects of treatment length on the outcomes four different subgroups were considered based on 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 analyzed. Exposure was measured as the time (in days) since the first prescription.

Information on comorbilities (ICPC-2 codes) and use of other medications (ATC codes) was obtained. Cumulative total days of treatment was calculated for each individual drug. 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 odds ratios (ORs) and 95 percent confidence intervals (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 adjusted only for matching variables. A second model adjusted additionally for smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, thyroid disease, and use of PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, corticosteroids (no use, <=1 yr, >1 yr), 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 was more prevalent in cases than in controls (table 1).

Ever use of bisphosphonates was more frequent in cases than in controls, 13 (29.6%) vs 23 (10.5%) yielding to an adjusted OR = 4.30 (95%CI, 1.55-11.9). Within ever users no apparent difference was observed between current, recent or past users, although numbers were quite small. A duration-dependent association

was suggested, with higher risk among those with longer exposure to bisphosphonates (> 3 years, OR = 9.46 (95%CI, 2.17-41.3) (table 2). The results by individual drugs are not shown because of insufficient sample size.

DISCUSSION

Key results

Our findings show an increase of atypical fracture risk among *ever users* of bisphosphonates vs *never users*, and a distinct duration-response association, with higher risk among women using bisphosphonates for longer time period. Results did not vary for bisphosphonate use timing (current use, recent use, 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 the overall cumulative exposure expresed 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, with a lower risk for bone fractures compared to Anglo-Saxon or Northern European countries. It could be hypothesized 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 4-fold higher risk. In this study an association between long-term use and higher risk was also observed. In two cohort studies 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 longer duration of bisphosphonate use.[24]

Bisphosphonates induce apoptosis of the osteoclasts and inhibit bone resorption. However, during the normal process of bone remodeling 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 bone structure. Biologically, this makes it 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 type 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 mineralization leading to increased 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 determined that atypical lesions are more frequent in femur regions of maximal tension loading.[26] Thereby there is 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 confidence intervals in the estimates of association.. Also we relied on prescription data to determine 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.

Bone mineral density 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 prevalence of previous fractures might confound the association between bisphosphonate use and risk of fracture. In order to minimize 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.

Acknowledgements

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TITLE

ORAL BISPHOSPHONATES ARE ASSOCIATED WITH INCREASED RISK OF SUBTROCHANTERIC AND DIAPHYSEAL FRACTURES IN ELDERLY WOMEN

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ARTICLE SUMMARY

Article Focus

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

Key messages

. Bisphosphonate use was associated with an increased risk of atypical femoral fractures in elderly women

. A higher risk among long-term bisphosphonate users was observed.

Strengths and limitations

. The main strength is that the observed odds ratios indicate a strong association between bisphosphonate use and increased atypical femoral fracture risk that 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.

ABSTRACT

Background: Case reports and a few epidemiological studies have shown an increased risk of atypical femoral fractures associated with bisphosphonate use. The evidence is, however, scarce and more formal studies are needed.

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

Methods:
Design. Nested case-control study
Setting. The study was performed in a general practice research database in Spain.
Exposures. Use of oral bisphosphonates any time before the occurrence of atypical fractures among cases or the corresponding index date among controls. Bisphosphonate use was categorized as ever vs 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 atypical femoral fracture (subtrochanteric or diaphyseal), recorded in the BIFAP database between 01/01/2005 and 31/12/2008, and with at least one year of follow-up before the index date. All cases were validated. For each case, 5 age- and calendar year-matched controls without history of hip or atypical fracture were randomly selected from the database.
Statistical analysis. OR and 95%CI of atypical femoral fracture by bisphosphonate use were 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 (1.55-11.9) in ever vs never users of bisphosphonates. The risk increased with long-term use, with an OR of 9.46 (2.17-41.3) comparing those using bisphosphonates over 3 years vs 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.

INTRODUCTION

Background

In 2005, *Odvina* et al published the first paper warning about the potentially harmful effects of alendronate due to suppression of bone remodelling.[1] Spontaneous fractures were observed in 9 patients receiving long-term treatment with the drug (between 3-8 years). It was hypothesized 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 inter-trochanteric 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 five 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 and 47-fold higher, respectively) while a recent case-control study showed a 3-fold increase in bisphosphonate users.[20] More studies in different populations with sufficient sample size 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 use of bisphosphonates and risk of subtrochanteric or diaphyseal fractures among women aged 65 years or older in a Mediterranean population. We hypothesized 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 Pharmacoepidemiologic 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 computerized medical records of >3.2 million patients attended by more than 1,800 primary care physicians throughout Spain. It includes anonymized 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 01/01/2005 and 31/12/2008, and with at least 1 year of follow-up in BIFAP before the event date. Pre-selected 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 hospitalization 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, 5 controls with no history of hip fracture at the time of the index date of their corresponding case were selected, matched by same age and calendar year of enrolment in BIFAP.

Medication use and other covariates

Use of bisphosphonates before the index date was obtained from the computerized 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 vs never users. Ever users were those with at least one prescription, with no minimum duration. Ever users were also divided into *current users* (if most recent prescription lasted through index date or ended in the month before it), *recent users* (if most recent prescription ended between 1 and 6 months before index date) and *past users* (if most recent prescription ended more than 6 months before index date).

In order to assess the effects of treatment length on the outcomes four different subgroups were considered based on 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 analyzed. Exposure was measured as the time (in days) since the first prescription.

Information on comorbilities (ICPC-2 codes) and use of other medications (ATC codes) was obtained. Cumulative total days of treatment was calculated for each individual drug. 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 odds ratios (ORs) and 95 percent confidence intervals (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 adjusted only for matching variables. A second model adjusted additionally for smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, thyroid disease, and use of PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, corticosteroids (no use, <=1 yr, >1 yr), 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 was more prevalent in cases than in controls (table 1).

Ever use of bisphosphonates was more frequent in cases than in controls, 13 (29.6%) vs 23 (10.5%) yielding to an adjusted OR = 4.30 (95%CI, 1.55-11.9). Within ever users no apparent difference was observed between current, recent or past users, although numbers were quite small. A duration-dependent association

was suggested, with higher risk among those with longer exposure to bisphosphonates (> 3 years, OR = 9.46 (95%CI, 2.17-41.3) (table 2). The results by individual drugs are not shown because of insufficient sample size.

DISCUSSION

Key results

Our findings show an increase of atypical fracture risk among *ever users* of bisphosphonates vs *never users*, and a distinct duration-response association, with higher risk among women using bisphosphonates for longer time period. Results did not vary for bisphosphonate use timing (current use, recent use, 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 the overall cumulative exposure expresed 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, with a lower risk for bone fractures compared to Anglo-Saxon or Northern European countries. It could be hypothesized 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 o~~O~~ur results are similar to those obtained in the largest case-control study published so far[20] and show an overall 4-fold higher risk. In this study an association between long-term use and higher risk was also observed. In two cohort studies 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 longer duration of bisphosphonate use.[24]

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract. **OK**	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **OK**	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **OK**	
Objectives	3	State specific objectives, including any pre-specified hypotheses **OK**	
Methods			
Study design	4	Present key elements of study design early in the paper **OK**	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **OK**	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **OK** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case **OK**	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **OK**	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **OK**	
Bias	9	Describe any efforts to address potential sources of bias **OK**	
Study size	10	Explain how the study size was arrived at **OK**	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **OK**	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **OK**	
		(*b*) Describe any methods used to examine subgroups and interactions **OK**	
		(*c*) Explain how missing data were addressed **OK**	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed **OK**	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **OK**	
		(b) Give reasons for non-participation at each stage Not applicable	
		(c) Consider use of a flow diagram Not applicable	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **OK**	
		(b) Indicate number of participants with missing data for each variable of interest **OK**	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure **OK**	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **OK**	
		(*b*) Report category boundaries when continuous variables were categorized **OK**	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **OK**	
Discussion			
Key results	18	Summarise key results with reference to study objectives **OK**	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **OK**	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **OK**	
Generalisability	21	Discuss the generalisability (external validity) of the study results **OK**	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **OK**	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.