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Increasing Occurrence of Atypical Femoral Fractures Associated With Bisphosphonate Use

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Background: Current evidence suggests that there is an association between bisphosphonate therapy and atypical femoral fractures, but the extent of this risk remains unclear.

Methods: Between 1999 and 2010, a total of 477 patients 50 years and older were hospitalized with a subtrochanteric or femoral shaft fracture at a single university medical center. Admission radiographs and medical and treatment records were examined, and patients were classified as having atypical or classic femoral fractures. A random sample of 200 healthy individuals without femoral fracture were also identified. Multivariate logistic regression was used to assess the association of bisphosphonate use and atypical femoral fracture, and the incidence rates of each type of fracture over time were calculated.

Results: Thirty-nine patients with atypical fractures and 438 patients with classic fractures were identified. Of the patients with atypical fractures, 32 (82.1%) had been treated with bisphosphonates compared with 28 (6.4%) in the classic fractures group (odds ratios [OR], 66.9; 95% CI, 27.1-165.1) and 11.5% in the group without fracture (OR, 35.2; 95% CI, 13.9-88.8). Bisphosphonate use was associated with a 47% reduction in risk of classic fracture (OR, 0.5; 95% CI, 0.3-0.9). Considering the duration of use, the ORs (95% CIs) for atypical fractures were 35.1 (10.0-123.6) for less than 2 years, 46.9 (14.2-154.4) for 2 to 5 years, 117.1 (34.2-401.7) for 5 to 9 years, and 175.7 (30.0-1027.6) for more than 9 years compared with no use. A contralateral fracture occurred in 28.2% of atypical cases and in 0.9% of classic cases (OR, 42.6; 95% CI, 12.8-142.4). The incidence rate of atypical fractures was low (32 cases per million person-years) and increased by 10.7% per year on average.

Conclusions: Atypical femoral fractures were associated with bisphosphonate use; longer duration of treatment resulted in augmented risk. The incidence of atypical fractures increased over a 12-year period, but the absolute number of such fractures is very small.

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THE USE OF BISPHOSPHONATES has been shown to increase bone mineral density and to reduce vertebral and proximal femur fracture risk in patients with osteoporosis.[1-6] However, these drugs have a biological half-life that exceeds 10 years[7] and may induce long-lasting inhibition of bone remodeling,[8] which could affect the healing of "physiologic microcracks,"[9-12] causing clinically apparent stress fractures in areas with high mechanical stress loads, such as the outer cortex of the femoral shaft.[13]

Consistent with this hypothesis, several recent publications have reported the emergence of a new type of subtrochanteric and femoral shaft stress fractures, defined as atypical fractures,[14] occurring in patients who are receiving bisphosphonate treatment.[15-22] The radiographic features include a transverse fracture line originating at an abnormal thickening of the lateral cortex of the femoral shaft.[14] A sudden fracture with minimal or no trauma is often preceded by prodromal thigh pain for some weeks.[14,23]

See Invited Commentary at end of article

Currently, there is conflicting evidence regarding the association between bisphosphonate treatment and atypical femoral fractures. A meta-analysis of randomized intervention trials[24] and several registry studies[25,26] found no association between atypical fractures and this class of compounds. In contrast, a recent large registry-based case-control study suggested that the risk of atypical hip fracture was more than doubled when the medication was taken for longer than 5

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years as compared with transient use.[27] However, radiographs were not examined, and both cases and controls had received bisphosphonates. Another retrospective study reported an adjusted odds ratio (OR) of 33 for atypical fractures associated with bisphosphonate use.[28] However, that study focused only on the year 2008 and provided limited information concerning treatment duration. Accordingly, some questions remain unanswered, such as the magnitude of the association, whether there is a correlation with treatment duration, and whether the risk of atypical fracture is changing over time.

We conducted a case-control study of patients who sustained subtrochanteric or femoral shaft fractures over a 12-year period. We compared the characteristics of patients with atypical fractures with those of patients with classic fractures of the subtrochanteric or femoral shaft area (hereafter known as classic fractures) and individuals without femoral fractures. The objective of the study was to evaluate the association between fracture pattern and bisphosphonate treatment. Also, we examined incidence trends of classic and atypical femur fractures between January 1999 and December 2010.

METHODS

STUDY DESIGN AND POPULATION

This case-control study included all patients 50 years of age and older who were admitted to the level I trauma center of a single university hospital (University Hospitals of Geneva, Geneva, Switzerland) with a fracture of the subtrochanteric or femoral shaft area between January 1, 1999, and December 31, 2010. Our institution is the reference trauma and general hospital for a population of 440 000 inhabitants and receives more than 95% of all the femur fractures occurring in a well-defined area.[29] We selected 2 major fracture subtypes as defined by the *International Statistical Classification of Diseases, 10th Revision*, including femoral subtrochanteric fractures (S72.2) and femoral shaft fractures (S72.3). We excluded patients with fractures resulting from high-energy trauma (eg, road traffic injuries, falls from more than standing height); fractures caused by tumors (either metastatic or primary) or documented Paget disease of bone; fractures involving an implant within the fracture line; and intraoperative femoral shaft fractures. Patients with conditions that might be associated with altered bone integrity, such as osteomalacia, osteopetrosis, hypercalcemia, hyperparathyroidism, celiac disease, and renal osteodystrophy, also were not included. As an additional control group, we identified individuals 50 years and older with no history of femoral fracture. Our study was approved by the Hospital Research Ethics Committee (protocol NAC-10-064R). An informed consent was obtained from all patients contacted by telephone.

DATA SOURCES

All hospitalizations (events) were retrieved from our university hospital's Medical and Economic Analysis Database, which provides detailed diagnostic, chronological, and procedural information regarding all hospital admissions since 1999. We used our institution's Computerized Patient Record System, which backs up a complete list of hospital admissions, procedures, hospital course, and discharge reports, including drug prescriptions and digitized radiographs for every patient. The population count was obtained for each year from the cantonal office of statistics.

CASE AND CONTROL DEFINITIONS

All patients (N=477) presenting with an initial subtrochanteric (S72.2) or femoral shaft (S72.3) fracture during the study period were identified as having either atypical fractures (cases) or classic fractures (controls) based on admission standard radiographs of the entire femur. Femur radiographs for every patient were independently examined by 2 trained physicians (R.P.H.M. and R.E.P) who were blinded to patient characteristics. Atypical fractures were characterized according to the criteria listed in the American Society of Bone and Mineral Research task force report.[14] Briefly, the atypical fracture pattern included a transverse or short oblique fracture line originating at the lateral femoral cortex between the lesser trochanter and the distal metaphysis. Fractures in the same location but of different appearance (spiral, wedge, segmental, or complex irregular) were categorized as classic fractures. The occurrence of a fracture line or a complete fracture occurring within the same area of the contralateral femur was looked for radiographically in both groups. Patient count, as opposed to fracture count, was considered for all analyses in this study. The first fracture was considered the reference. Discrepancies between the 2 physicians were resolved by consensus.

A second control group of 200 individuals 50 years and older with no history of femoral fracture was randomly chosen from an independent database that prospectively collects information on genetic determinants of bone microstructure in the normal population in the same institution. Detailed information regarding the use of bisphosphonates as well as other medications (with the exception of proton pump inhibitor use) was available for all healthy control patients.

EXPOSURE ASSESSMENT

The occurrence of previous or current bisphosphonate treatment (alendronate, risedronate, pamidronate, ibandronate, etidronate, or zoledronic acid) was assessed by detailed examination of the medication list included in the computerized hospital medical records. This assessment was done for each patient who presented with a subtrochanteric fracture (S72.2), a femoral shaft fracture (S72.3), or no fracture (n=677). When a patient was listed as a bisphosphonate user, this information, as well as the duration of use, was verified by telephone contact with each patient and/or their primary care physician.

POWER

We sought to identify an OR of 10 or greater. With a type 1 error rate of 0.05, a power of 0.9, and an expected prevalence of bisphosphonate use of 10% among controls, 30 cases and 30 controls would have been required. However, as we wanted to adjust the analysis for potential confounders and to examine the duration of bisphosphonate use, we included all eligible patients who were treated during the study period.

STATISTICAL ANALYSIS

The differences between atypical fracture cases, classic fracture cases, and nonfracture controls were analyzed using univariate and multivariate logistic regression (**Table 1**) and χ^2 tests (**Table 2**). The duration of bisphosphonate use was categorized as none, less than 2 years, 2 to 5 years, 5 to 9 years, and 9 years or more. An exact 2-sided *P* value of less than .05 was considered statistically significant. To verify the concor-

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Table 1. Risk Factors for Subtrochanteric and Femoral Shaft Atypical Fractures: Univariate and Multivariate Logistic Regression Analysis

Variable	Fracture, No. (%)		Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)[a]	*P* Value
	Atypical (n = 39)	Classic (n = 438)				
Bisphosphonate use	32 (82.1)	28 (6.4)	66.9 (27.1-165.1)	<.001	69.1 (22.8-209.5)	<.001
Type of bisphosphonate[b]						
Alendronate	27 (69.2)	21 (4.8)	44.7 (19.9-100.3)	<.001	NA	NA
Risedronate	1 (2.6)	2 (0.5)	5.7 (0.5-64.7)	.16	NA	NA
Pamidronate	3 (7.7)	2 (0.5)	18.2 (2.9-112.3)	.002	NA	NA
Ibandronate	1 (2.6)	2 (0.5)	5.7 (0.5-64.7)	.16	NA	NA
Etidronate	0 (0.0)	1 (0.2)	NA	NA	NA	NA
Zoledronic acid	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Duration of bisphosphonate use, y[b]						
None	7 (17.9)	410 (93.6)	1 [Reference]	NA	NA	NA
<2	6 (15.4)	10 (2.3)	35.1 (10.0-123.6)	<.001	NA	NA
2-5	8 (20.5)	10 (2.3)	46.9 (14.2-154.4)	<.001	NA	NA
5-9	12 (30.8)	6 (1.4)	117.1 (34.2-401.7)	<.001	NA	NA
≥9	6 (15.4)	2 (0.5)	175.7 (30.0-1027.6)	<.001	NA	NA
Vitamin D use	19 (48.7)	93 (21.2)	3.5 (1.8-6.9)	<.001	0.5 (0.2-1.5)	.24
Corticosteroid use	7 (17.9)	24 (5.5)	3.8 (1.5-9.4)	.004	2.5 (0.6-10.0)	.21
Proton pump inhibitor use	22 (56.4)	177 (40.4)	1.9 (1.0-3.7)	.06	1.8 (0.7-4.6)	.20
Female sex	36 (92.3)	319 (72.8)	4.5 (1.4-14.8)	.01	3.7 (0.8-18.4)	.11
Age group, y						
50-69	11 (28.2)	86 (19.6)	13.2 (1.7-104.1)	.01	19.5 (1.8-211.6)	.01
70-79	16 (41.0)	86 (19.6)	19.2 (2.5-147.4)	.005	23.8 (2.3-251.0)	.008
80-89	11 (28.2)	163 (37.2)	7.0 (0.9-54.6)	.07	7.5 (0.7-78.0)	.09
90-102	1 (2.6)	103 (23.5)	1 [Reference]	NA	1 [Reference]	NA
Contralateral fractures[b]	11 (28.2)	4 (0.9)	42.6 (12.8-142.4)	<.001	NA	NA

Abbreviations: NA, not applicable; OR, odds ratio.
[a]The multivariate model included bisphosphonate use, vitamin D use, corticosteroid use, proton pump inhibitor use, and sex (as binary variables) and age (as a categorical variable).
[b]These variables were not included in the multivariate model because they were colinear with bisphosphonate use (contralateral fractures) or partly redundant (duration of use and type of bisphosphonate).

Table 2. Characteristics of Patients With Atypical and Classic Fractures Among Bisphosphonates Users and Nonusers: Univariate Analysis

Variable	Atypical Fracture Cases (n = 39)			Classic Fracture Cases (n = 438)		
	Users of Bisphosphonates, No. (%) (n = 32)	Nonusers of Bisphosphonates, No. (%) (n = 7)	*P* Value[a]	Users of Bisphosphonates, No. (%) (n = 28)	Nonusers of Bisphosphonates, No. (%) (n = 410)	*P* Value[a]
Female sex	30 (93.8)	6 (85.7)	.46	25 (89.3)	294 (71.7)	.05
Age group, y			.97			.76
50-69	9 (28.1)	2 (28.6)		5 (17.9)	81 (19.8)	
70-79	13 (40.6)	3 (42.9)		5 (17.9)	81 (19.8)	
80-89	9 (28.1)	2 (28.6)		13 (46.4)	150 (36.6)	
90-102	1 (3.1)	0		5 (17.9)	98 (23.9)	
Vitamin D use	18 (56.3)	1 (14.3)	.09	21 (75.0)	72 (17.6)	<.001
Corticosteroid use	5 (15.6)	2 (28.6)	.59	6 (21.4)	18 (4.4)	.002
Proton pump inhibitor use	19 (59.4)	3 (42.9)	.68	12 (42.9)	165 (40.2)	.84

[a]Global *P* value for the categorical variable.

dance between observed and expected rates, we applied a Hosmer-Lemeshow statistical test. We used κ statistics to determine interobserver agreement of fractures categorization between the 2 physicians.

We used Poisson regression to obtain temporal trends in fracture incidence rates between 1999 and 2010, separately for classic femoral fractures, and atypical fractures. The denominator was the state population 50 years and older. The model was

$$\log(\text{Events}_{\text{Year}}) = \log(\text{Population}_{\text{Year}}) + b_0 + b_1 \times \text{Year}.$$

The regression coefficients were interpreted as follows: exp (b_0) is the incidence rate in the reference year (1999), and $100 \times [\exp(b_1) - 1]$ is the relative annual increase in inci-

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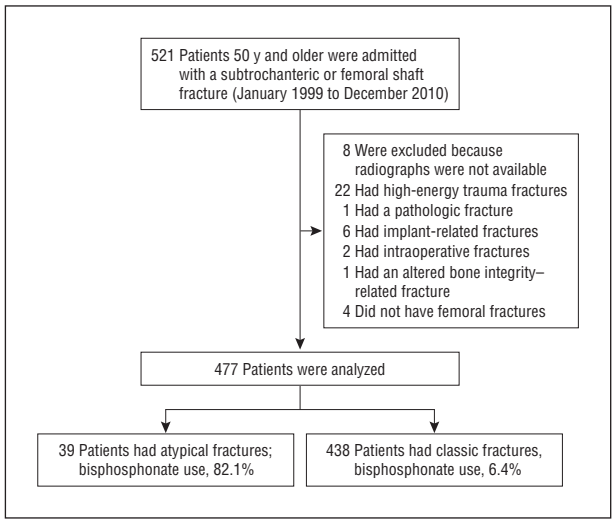

Figure 1. Identification of atypical fractures of the subtrochanteric and femoral shaft area in the study population.

dence averaged over the 12-year observation period, in percent. Differences in incidence trends were tested using Poisson regression models with interaction terms. To compare atypical and classic fractures, we introduced a variable called *type* (coded as 1 if atypical, 0 if classic) and the interaction between type and year, as follows:

$$\log(\text{Events}_{\text{Year}}) = \log(\text{Population}_{\text{Year}}) + b_0 + b_1 \times \text{Year} + b_2 \times \text{Type} + b_3 \times \text{Year} \times \text{Type}.$$

In this model, b_1 captures the annual change in classic fracture rates (slope); b_2 captures the difference in fracture rates in the reference year (1999); and b_3 captures the difference in slopes between atypical and classic fracture rates. We used the same model to obtain a temporal trend in bisphosphonate user prevalence in all patients with classic and atypical fractures.

RESULTS

Between 1999 and 2010, a total of 477 eligible patients were admitted with a first subtrochanteric or femoral shaft fracture (**Figure 1**). Based on a systematic review of standard admission radiographs, we identified 39 patients with an atypical fracture (atypical group) and 438 patients with a classic fracture (classic group). The interobserver agreement for fracture categorization was excellent[30]: κ, 0.96 (95% CI, 0.91-1.00).

A contralateral fracture occurred in 11 patients in the atypical group (28.2%) and 4 patients in the classic group (0.9%). The contralateral fracture was of the same type as the first fracture in all 15 patients. In the atypical group, there were 8 complete and 3 incomplete contralateral fractures, all in patients treated with bisphosphonates. The OR for recurrence in patients with atypical fractures was 42.6 (95% CI, 12.8-142.4) when compared with patients with classic fractures.

CASE-CONTROL ANALYSIS

Among the 39 patients who had atypical fractures, 32 (82.1%) had been treated with bisphosphonates. In the classic fracture group, 28 (6.4%) had received bisphosphonates (Table 1). The crude OR was 66.9 (95% CI, 27.1-165.1). Taken separately, treatment with alendronate, risedronate, pamidronate, and ibandronate was associated with augmented ORs for atypical fractures. Other univariate risk factors for atypical fractures included female sex, younger age, and use of vitamin D or corticosteroids. The OR of 1.9 (95%, CI 1.0-3.7) with proton pump inhibitor use was not statistically significant.

After adjustment for potential risk factors (vitamin D, corticosteroids, proton pump inhibitor, sex, and age), use of bisphosphonates (any vs none) was associated with an OR of 69.1 (95% CI, 22.8-209.5) for an atypical fracture compared with the classic fracture group. Of note, none of the potential confounders was statistically significant in the multivariate model except for the following age groups: 50 through 69 years and 70 through 79 years (Table 1). The Hosmer-Lemeshow test result was not significant ($P = .48$).

The characteristics of the patients with atypical and classic fractures among bisphosphonate users and nonusers are shown in Table 2. Among the patients who received bisphosphonates, the atypical fracture group had a longer treatment period than the classic fracture group (mean [SD], 5.1 [3.1] years vs 3.3 [2.6] years; $P = .02$). Once categorized by duration of treatment, the ORs (95% CIs) for an atypical fracture vs a classic fracture were 35.1 (10.0-123.6) for less than 2 years, 46.9 (14.2-154.4) for 2 to 5 years, 117.1 (34.2-401.7) for 5 to 9 years, and 175.7 (30.0-1027.6) for 9 years or more compared with no use.

The 200 patients without femoral fractures were aged 63 to 67 years (mean age, 65 years), and 157 (78.5%) were women. Twenty-three (11.5%) were bisphosphonate users; 71 (35.5%) had been treated with vitamin D; and 6 (3.0%) had been treated with corticosteroids. Comparing the atypical fracture group with the nonfracture controls, bisphosphonate treatment was associated with an OR of 35.2 (95% CI, 13.9-88.8; $P < .001$) for atypical fracture. The ORs were 1.7 (95% CI, 0.9-3.4; $P = .12$) for vitamin D use, 7.1 (95% CI, 2.2-22.4; $P = .001$) for corticosteroid use, and 3.3 (95% CI, 1.0-11.2; $P = .06$) for female sex. After adjustment for these potential risk factors, the use of bisphosphonates was associated with an OR of 49.7 (95% CI 15.9-155.1; $P < .001$) for an atypical fracture. The adjusted ORs were 0.3 (95% CI, 0.1-1.0; $P = .05$) for vitamin D use, 5.9 (95% CI, 1.1-30.4; $P = .03$) for corticosteroid use, and 1.7 (95% CI, 0.3-10.6; $P = .59$) for female sex. The OR was 0.5 (95% CI, 0.3-0.9; $P = .03$) for bisphosphonate use when patients with classic fractures were compared with individuals without fractures, indicating that bisphosphonate therapy was associated with a 47% reduction in fracture risk.

INCIDENCE RATES AND TEMPORAL TREND

Averaged over the 12 years of observation, the incidence rates were 357 cases per million person-years for classic fractures and 32 cases per million person-years for atypical fractures. Between 1999 and 2010, the overall incidence rate of classic fractures remained stable, while the incidence of atypical fractures increased (**Figure 2**). In Poisson regression models, the mean annual change in incidence was +0.4% (95% CI, −2.3% to +3.1%;

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P = .78) for classic fractures and +10.7% (95% CI, +1.2% to +20.3%; P = .03) for atypical femoral fractures. The temporal trend of atypical fractures differed significantly from the temporal trend of classic fractures (difference, +10.3% per year; 95% CI, +0.4% to +20.3%; P = .04). Between 1999 and 2010, the prevalence of bisphosphonate users (mean [SD], 19.8% [7.5%]) remained stable in our study population, and the mean annual change was −1.5% (95% CI, −5.2% to +2.2%; P = .43).

COMMENT

The primary objective of our study was, first, to evaluate the association between bisphosphonate treatment and atypical femoral fractures and, second, to compare incidence trends of these fractures over the last decade. The key findings were (1) a significantly elevated risk of atypical femoral fracture among bisphosphonate users; (2) an increasing risk of atypical fracture with longer duration of use and no evidence of a threshold or a plateau; and (3) an increasing incidence of such fractures over the last decade. Our results are in agreement with those of others[27,28,31] but contradict recent studies suggesting that the use of bisphosphonates does not increase the risk of atypical fractures.[24-26]

It is interesting to note that bilateral fractures were frequent in patients with atypical fractures. This finding strongly supports the need for radiographic examination of the contralateral femur in all patients presenting with an atypical fracture, whether or not symptomatic, to decide about treatment, including perhaps possible prophylactic internal fixation if a stress fracture pattern is detected.

We observed an incidence rate of 32 atypical cases per million person-years and noted an increasing occurrence of such cases over time. This incidence rate is very low; there were 11 times more classic fractures during the same period. Furthermore, if we consider a 50% reduction of proximal femur and classic fractures (supported by our results and by literature[1,6]) and a prescription rate of approximately 10% in the population at risk,[28] the absolute benefit to risk ratio of bisphosphonate treatment would remain clearly favorable, notably keeping in mind that the use of bisphosphonates would also reduce vertebral fractures by 40% to 70% and wrist fractures by 50%.[1,6]

The strengths of our study include (1) the large number of patients; (2) the fact that patients were treated at the same institution over a 12-year period; (3) an accurate radiographic evaluation of all subtrochanteric and femoral shaft fractures; and (4) detailed information on temporal trends, duration of treatment, and bilateral fractures. However, we must acknowledge some limitations. First, a retrospective design does not allow definitive conclusions on causality. Second, although we adjusted for several available cofactors, other confounding or bias cannot be excluded. In particular, we did not have sufficient information concerning bone density, bone turnover, use of other medications, smoking history, body mass index, and exercise history to include into the analyses. Third, although associations and trends were statistically significant in our study, the small number of atypical fractures resulted in large CIs in the computation of ORs and year-to-year variability in the temporal trend of atypical fractures.

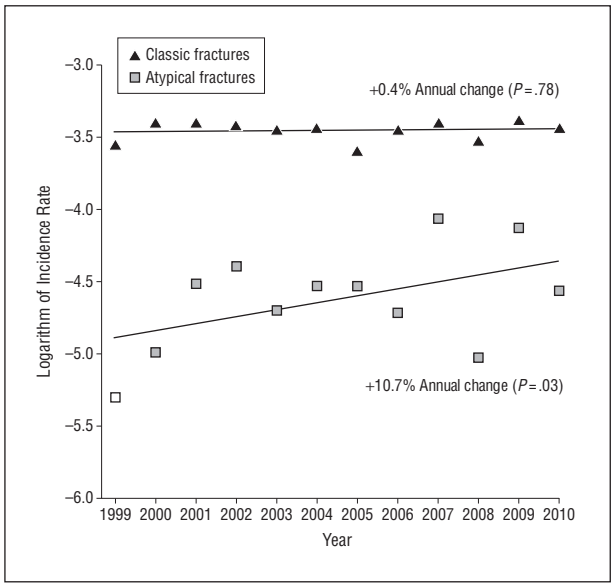

Figure 2. Incidence rates of classic subtrochanteric or femoral shaft fractures and atypical fractures among residents of the state 50 years and older. The white square in 1999 stands in for an incidence rate of 0 (the logarithm is negative infinity).

Another point that was not directly addressed in this study concerns the pathogenetic mechanism of atypical fractures. A mechanistic hypothesis based on the work of Perren[32,33] might be proposed. He described interfragmentary strain at a fracture site as a variable defined as the displacement divided by the interfragmentary distance (Strain = Motion/Gap). Ideally, the interfragmentary strain should remain within limits of 1% to 2% to allow local osteoblast proliferation and repair of the crack. In the hypothetical situation of constant interfragmentary motion, the healing process of physiologic microcracks requires a widening of the interfragmentary distance to bring local strain within these narrow limits of 1% to 2%. This task is performed by osteoclasts. In cases of osteoclast dysfunction,[34] the interfragmentary distance remains too small and the strain excessively high, thus failing to allow the physiologic repair process to take place. The perpetuation of this dysfunction may therefore lead to a clinically apparent stress fracture.

Nevertheless, important issues still require clarification. For instance, why do only a few patients who are being treated with bisphosphonates present with atypical fractures? And why do some others present with atypical fractures without any history of bisphosphonate use?[35,36] Accordingly, a search for other potential cofactors should be a priority. Identification of patients who are at high risk for bisphosphonate-associated fractures would allow a targeted prescription of this class of drugs and a reduction or avoidance of atypical fractures in the future. A multifactorial model of atypical fractures also opens the door to the possibility of pathogenetic mechanisms not involving bisphosphonates.

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In conclusion, we have demonstrated that the association between bisphosphonate treatment and the occurrence of atypical fractures of the femur is highly likely and that the duration of such treatment significantly correlates with augmented risk. However, the incidence rate was very low, and the absolute benefit to risk ratio of bisphosphonate use remains positive. The identification of patients who are at risk seems to be of crucial importance to reduce this complication in the future.

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Author Contributions: Drs Meier, Rizzoli, and Peter had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Meier, Stern, Rizzoli, and Peter. *Acquisition of data:* Meier and Peter. *Analysis and interpretation of data:* Meier, Perneger, Rizzoli, and Peter. *Drafting of the manuscript:* Meier, Rizzoli, and Peter. *Critical revision of the manuscript for important intellectual content:* Meier, Perneger, Stern, Rizzoli, and Peter. *Statistical analysis:* Meier, Perneger, and Rizzoli. *Administrative, technical, and material support:* Meier and Peter. *Study supervision:* Stern, Rizzoli, and Peter.
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INVITED COMMENTARY

ONLINE FIRST

Atypical Femoral Fracture Risk in Patients Treated With Bisphosphonates

There is increasing evidence that the use of bisphosphonates to prevent osteoporotic fractures, particularly long-term use, is associated with an increased risk of unusual fractures of the proximal femur. Numerous case reports of these "atypical" fractures of the femur among bisphosphonate-treated women have appeared over the last 5 years or more.[1,2] A case definition for atypical femur fractures has now been proposed[3] that includes subtrochanteric (below the lesser trochanter) or diaphyseal (above the distal metaphysis) location, transverse or nearly transverse "chalklike" fracture line (as opposed to the more typical spiral or comminuted fractures), and paucity of trauma. Additional features may include the presence of prodromal thigh pain, bilateral involvement, cortical thickening, and the presence of other selected diseases (such as rheumatoid arthritis or diabetes) or medication use (such as corticosteroids or proton pump inhibitors). Some reports, but certainly not all, suggest marked suppression of bone turnover as assessed by bone turnover markers and iliac crest histomorphometry.[1] Even if causally related, these atypical fractures must be quite rare among osteoporotic women treated with bisphosphonates, as a recent pooled analysis of 3 large clinical trials (FIT, FLEX, and HORIZON) with up to 10 years of follow-up[4] found that all types of subtrochanteric and diaphyseal fractures were infrequent and similar among placebo- and bisphosphonate-treated women. Although these findings are reassuring, important limitations were that relatively few women received more than 5 years of bisphosphonate treatment, information on atypical features was not specifically collected, and only radiographic reports were reviewed. Clearly, because atypical subtrochanteric fractures occur infrequently, they are unlikely to be easily studied in randomized trials, and other study designs will be necessary.

Large observational studies have also examined the relationship between bisphosphonate use and subtrochanteric or diaphyseal fractures. For example, Abrahamsen et al[5] used Danish administrative data to examine the relationship between bisphosphonate use and subtrochanteric or diaphyseal femur fractures among 39 567 alendronate users and 158 268 nonusers. As would be expected because of their higher pretreatment risk, alendronate users were more likely to suffer classic hip fractures than nonusers (hazard ratio, 1.5; 95% CI, 1.4-1.5), and a similar increase was observed for subtrochanteric and diaphyseal femur fractures (hazard ratio, 2.0; CI, 1.8-2.3). The observation that subtrochanteric and diaphyseal fracture risks were similar among individuals receiving short-term (several months) and long-term (5-10 years) alendronate treatment was somewhat reassuring, but the study was unable to specifically identify which of the fractures included were atypical. Contrary to the results of Abrahamsen and colleagues, a large retrospective cohort study from a California Health Maintenance Organization linking pharmacy and radiographic data[6] found that among 15 000 femur fractures identified between 2007 and 2009, radiographic review identified 135 subtrochanteric and diaphyseal fractures with atypical features. Nearly all of the individuals with atypical femoral fractures had taken bisphosphonates (97%), and longer duration of use further increased the risk. Although only presented in abstract form and not yet published, these preliminary data appear to support a causal relationship between bisphosphonate use and atypical femoral fractures.

The case-control study by Meier et al[7] in this issue of the *Archives* adds further data suggesting that the association between bisphosphonate use and atypical femur fractures is causal. These Swiss investigators reviewed radiographs from 477 individuals with subtrochanteric or proximal femoral shaft fractures collected between 1999 and 2010 at a single center and identified 39 with atypical features (0.7% of all femur fractures). For comparison, the investigators used 2 groups: individuals with typical femur fractures and a completely separate group of individuals without fractures. Of the individuals with atypical fractures, 82% reported bisphosphonate use compared with only 6% in the typical fracture group and 12% in the group without fractures. Furthermore, Meier and colleagues found that longer use of bisphosphonates (5-9 years) was associated with a greater risk of atypical fractures (odds ratio, 117; 95% CI, 34-402) compared with shorter use (<2 years) (odds ratio, 35; 95% CI, 10-124). Although Meier and coauthors did not address the

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