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Diaphyseal femur fractures associated with bisphosphonate use

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Objective: The aim of this study was to investigate the association of bisphosphonate exposure with low-energy, non-articular femur fractures.

Methods: The electronic records of 106 patients over the age of 55 years who sustained low-energy non-articular femur fractures and were treated within an integrated health system were examined. Patients were identified through a prospective registry and all fractures were classified anatomically. Cases were matched with control patients without fracture, and prescription orders were examined to assess drug exposures. Conditional logistic regression tested for a significant association between bisphosphonate exposure and fracture.

Results: Thirteen of the 106 cases (12%) and 76 of 804 controls (9%) received at least one year of prescriptions for bisphosphonates prior to fracture. Odds ratio for bisphosphonate exposure as a risk factor was 1.52 (95% confidence interval: 0.76 to 3.05), suggesting no statistically significant association (p=0.24). Results were similar when four-year exposure or alendronates only were studied.

Conclusion: Bisphosphonate exposure was not associated with non-articular femur fracture in this case-control study. We suggest that the majority of low-energy, geriatric femur fractures are not associated with bisphosphonate exposure.

Key words: Alendronate; bisphosphonate; femur diaphysis; insufficiency fracture; osteoporosis.

Subtrochanteric or diaphyseal femoral shaft fractures are extremely rare. A recent study using a Danish population-based registry estimated an incidence rate between 0.27 and 2.75 per 1000 patient-years in untreated women over the age of 60, with only 40% of these attributed to low-energy trauma. Several case series and reports documenting patients exposed to prolonged bisphosphonate therapy and those presenting with low-energy diaphyseal femoral stress fractures were initiated in 2005.[1-12] These studies proposed a causal link between the two phenomena, hypothesizing that prolonged suppression of osteoclast function results in a low bone turnover state and subsequent fatigue fractures with a characteristic pattern.

In 2010, an American Society for Bone and Mineral Research (ASBMR) task force examined similar studies encompassing a total of 310 women and found that 96% had long-term exposure to bisphosphonates.[13] This task force's report recommended a provisional case definition of 'atypical femoral fractures' (i.e., low-

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energy, non-comminuted, transverse or short oblique fractures located between the lesser trochanter and the supracondylar flare) for use in future studies. They concluded that, despite the lack of a causal association between bisphosphonates and atypical fractures, physicians should be made aware of the potential through a change in drug labeling. On the basis of these recommendations, the U.S. Food and Drug Administration (FDA) changed labeling requirements and issued a medication guide in September 2010, warning patients and physicians about the possible increased risk of diaphyseal femoral fracture from bisphosphonates.[14]

To date, there has been very limited evidence supporting a causal link between bisphosphonate use and diaphyseal fractures based on either prospective or controlled studies. The relative rarity of low-energy diaphyseal femur fractures in the mature adult population and the increased risk of fracture associated with osteoporosis confound many attempts to more completely understand the problem.

The purpose of our study was to investigate the association of bisphosphonate exposure with diaphyseal femur fracture in a large, primary-care-based population, without restricting subjects to bisphosphonate users.

Patients and methods

Patients aged 55 years and older receiving medical care from the Geisinger Health System (GHS) between January 1, 2004 and October 31, 2010 were eligible for this study. The GHS is a large integrated health system located in northeast and central Pennsylvania, serving a 41-county area with approximately 2.5 million people and providing care to approximately 600,000 unique patients annually at 38 outpatient clinics and three hospitals. The average duration of care for patients in the system exceeds ten years. In 1996, GHS implemented electronic health records (EHR, EpicCare), which has been the sole-source ambulatory record for all patients since 2001. All outpatient encounters and related prescriptions are captured in the EHR and both elements are linked to an International Classification of Diseases (ICD-9) diagnosis code. The Department of Orthopedics also maintains an IRB-approved, prospective trauma registry database in which all treated fractures are prospectively classified according to the AO/Orthopaedic Trauma Association (AO/OTA) radiographic system by an orthopedic fellow who is blinded to other treatment details such as drug exposure.

All patients treated for acute, low-energy intertrochanteric or diaphyseal femur fractures (AO/OTA 31A-3, 32A, 32B, or 33A-1) between 2005 and 2010 at two hospitals within the health system were identified via the registry. Patients with end-stage renal disease on dialysis, patients sustaining high-energy fractures and those with neoplastic or infectious disease of bone were excluded from consideration. All cases were required to have had additional outpatient encounters within the health system prior to and following their surgical treatment.

A control population was selected from all 140,649 patients greater than 55 years of age receiving outpatient care within the integrated health system during the study period. Control patients with femur fractures or those in end-stage renal disease on dialysis were excluded. When examining comorbidities, a patient was defined as having a comorbid disease if either a problem list entry or two separate encounters linked to the appropriate ICD-9 codes appeared in the EHR prior to the date of interest. Table 1 lists diagnosis codes used for each condition of interest. A matched, control cohort was selected by randomly matching each case with up to 8 unique control subjects based on: (1) date of birth within 1 year; (2) same sex; (3) same length of pre-fracture observation period within 1 year; (4) same history of osteoporosis (yes or no); (5) same history of renal disease (yes or no); and (6) similar number of unrelated comorbidities, within ±1, from the following list: hypertension, stroke, acute myocardial infarction, congestive heart failure, osteoarthritis or rheumatoid arthritis, anemia and Alzheimer's disease. In each matched set of subjects, the case's date of femoral fracture was defined as the index date for analysis.

Table 1. ICD-9 diagnosis codes used to define comorbid diseases in case and control patients.

Disease	ICD-9 codes used
Acute myocardial infarction (AMI)	410., 411, 411.1, 411.8, 411.81, 411.89, 413, 413.9, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, V45.81, V45.82
Anemia	285.
Alzheimer's disease	331.
Congestive heart failure	425., 428.
Dialysis	V45.1
Femoral fracture, proximal or shaft	820.-821.
Hypertension	401.-405.
Osteoporosis	733.
Osteoarthritis or rheumatoid arthritis	714.-716.
Periprosthetic fracture	966.4, 966.43. 966.44
Renal disease	403.-404., 593.9, 585.-586.
Stroke	430.-434.

One hundred and twenty-six patients were identified to have been surgically treated for low-energy diaphyseal femoral fracture between 2005 and 2010. Thirteen patients (10%) had no outpatient appointments within the health system during the study period, and six patients (5%) had end-stage renal disease. These 19 subjects were excluded from further analysis, leaving 107 cases. As one case could not be matched to any control subjects, matching resulted in a case cohort of 106 subjects and a control cohort of 804 subjects. Table 2 shows the baseline characteristics of both cohorts. The two cohorts were very similar in age, sex, length of observation, and history of osteoporosis and renal disease. The case cohort had a lower mean number of unrelated comorbidities than the controls, but we considered this variable a low priority for matching.

Bisphosphonate exposure was determined based on the prescription order records in the EHR. Prescriptions for alendronate sodium, ibandronate sodium, pamidronate, risedronate sodium, or zoledronic acid were included. We defined short-term exposure as a patient receiving a minimum of two prescriptions for bisphosphonate spanning at least a one-year period prior to the index date. For analysis of long-term exposure, we considered only patients with 4 years of available records prior to the index date, and long-term bisphosphonate exposure was defined as multiple prescription orders spanning at least a four-year period. The percentages of bisphosphonate exposures in the two groups were examined, and conditional logistic regression (SAS 9.2 software) was used to test for the significance of whether prior exposure to bisphosphonate was associated with low-energy diaphyseal fracture, with $p<0.05$ considered significant.

Table 2. Baseline demographics and rates of case and control groups after matching. Each variable was compared between the cohorts using Wilcoxon two-sample tests, Student t-tests, or chi-square testing to yield p values for comparison.

	Cases (n=106)	Controls (n=804)	P value
Age in years, median (interquartile range)	78 (71-84)	78 (71-84)	0.87
Years of observation prior to fracture date, median (interquartile range)	2.1 (0.8-4.9)	2.2 (0.8-4.9)	0.89
% male	27	26	0.74
% with osteoporosis	42	40	0.65
% with renal disease	12	10	0.54
Number of unrelated comorbidities, mean (std. dev.)	2.5 (1.4)	2.8 (2.2)	<.001

Based on prior studies, we also repeated the above analysis using only alendronate prescription orders rather than orders for all bisphosphonates.[1-5,7-10] Because of related concerns that our results could be confounded by use of corticosteroids or hormone replacement therapy (HRT), we also examined both case and control cohorts for prior exposure to these two drugs using similar definitions to those described above for bisphosphonates. Finally, we retrospectively reviewed the radiographs of all cases to identify the subgroup with fractures having both major and minor features suggested by ASBMR and examined bisphosphonate exposure in this subgroup. The radiographic review was conducted by a co-author (KI) who was blinded to drug exposure status.

Results

Table 3 summarizes the patients with bisphosphonate exposure in each cohort and statistical results. Thirteen

Table 3. Numbers and percentages of patients in each cohort with exposure to bisphosphonate, alendronate or bisphosphonate combined with other drugs. Odds ratios express the increased risk of fracture in the case vs. control cohorts associated with drug exposure, using multiple definitions.

	Controls		Cases			
Risk factor	**N subjects**	**N subjects (%), with exposure**	**N subjects**	**N subjects (%), with exposure**	**Odds ratio [95% CI]**	**P value**
Any bisphosphonate						
Short-term (>1 year) exposure	804	76 (9%)	106	13 (12%)	1.52 [0.76-3.05]	0.24
Long-term (>4 year) exposure	225	25 (11%)	26	3 (12%)	0.92 [0.24-3.51]	0.91
Alendronate only						
Short-term (>1 year) exposure	804	46 (6%)	106	8 (8%)	1.47 [0.65-3.34]	0.36
Long-term (>4 year) exposure	225	16 (7%)	26	3 (12%)	1.57 [0.41-6.11]	0.51
Combined exposures						
Bisphosphonate and corticosteroid exposure (>1 year)	804	16 (2%)	106	3 (3%)	1.52 [0.43-5.34]	0.51
Bisphosphonate and hormone replacement therapy (HRT) exposure (>1 year)	804	2 (<1%)	106	0 (0%)	--	--

of the 106 case patients (12%) had exposure (>1 year) to bisphosphonate, compared with 76 of the 804 matched control patients (9%). Conditional logistic regression analysis estimated that the odds ratio for bisphosphonate exposure as a risk factor for fracture was 1.52 (95% confidence interval (CI): 0.76 to 3.05), suggesting no statistically significant association (p=0.24). Based on the width of this confidence interval, power analysis suggests that this study was adequately powered to detect a significant odds ratio of 2.0 or greater, implying that the true odds ratio is <2.0. Given the rarity of these fractures,[15] such an odds ratio would translate into a very small increase in the absolute risk of fracture (≤0.5%).

The percentages of cases and controls with long-term (>4 year) exposure to bisphosphonate were very similar as well (12% and 11%, respectively), and the odds ratio for long-term exposure as a risk factor was 0.92 (95% CI: 0.24 to 3.51), suggesting no statistically significant association (p=0.91). Restricting the analysis to alendronates only gave slightly different odds ratio estimates for short- or long-term bisphosphonate exposure as a risk factor for low-energy diaphyseal femoral fracture (1.47 to 1.57), although neither of these reached statistical significance (p=0.36 to 0.51).

A retrospective review of all cases identified 4 out of the 106 case subjects (4%) that displayed all three "minor features" of atypical femoral fractures identified in the ASBMR report plus prodromal pain (Figs. 1 and 2). Although the sample size of this subgroup was too small to allow statistical analysis, we note that 2 of the 4 patients had no prior prescription orders for bisphosphonates (despite having over five years of EHR records available prior to fracture), one patient had a single prescription order, and only one patient had multiple orders.

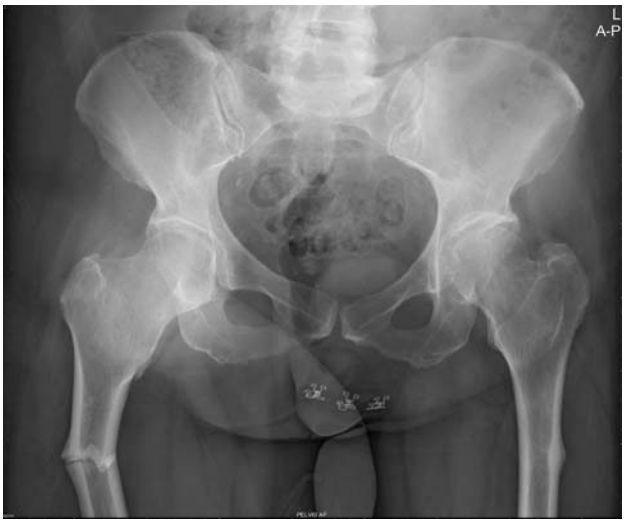

Fig. 1. Anteroposterior pelvis radiograph demonstrating bilateral, transverse subtrochanteric femur fractures in a 67-year-old woman with a history of osteoporosis and multiple hereditary osteochondromatosis.

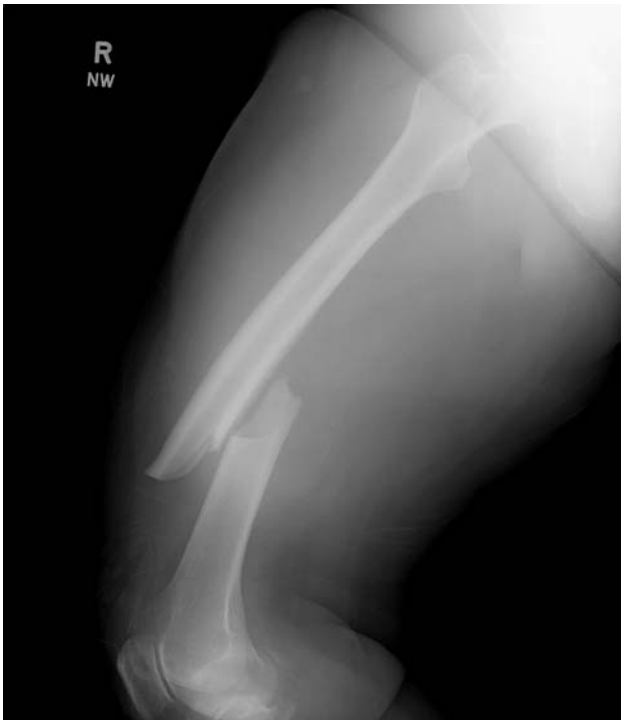

Fig. 2. Lateral femoral radiograph demonstrating an oblique diaphyseal femur fracture with cortical 'spike' and 'beaking' in a 69-year-old woman with a history of osteoporosis and bisphosphonate exposure.

Discussion

In this retrospective, case-controlled study of over 100 patients with low-energy diaphyseal femoral fractures, we noted that only a relatively small percentage (12%) had evidence of prior exposure to bisphosphonates and statistical analysis failed to show an association between drug exposure and the risk of these uncommon fractures. Secondary analyses focusing on longer-term (>4 year) drug exposure or alendronate use showed consistent results and analyses of bisphosphonate combined with other related drugs (corticosteroids or estrogens) did not suggest that their use confounded the main result.

Although results were not significant, the strength of our study was its case-control design in a large, primary-care based population of patients with and without fractures. It improved upon the existing estimates of risk in the literature, most notably the 95% confidence interval of 0.06 to 16.46 reported by Black et al.[16] who reviewed records of 14,195 women in three large, randomized placebo-controlled trials and identi-

fied 12 diaphyseal fractures. The authors found no significant increased risk of attributable to the drug but acknowledged the study was underpowered for definitive conclusions. Abrahamsen et al. compared the incidence of diaphyseal fracture in alendronate users with that in non-users in a large population-based registry and also concluded that there was no evidence of an increased risk of fracture of the subtrochanteric or diaphyseal femur with either short- or long-term use of a bisphosphonate.[15] These authors had limited fracture classification details whereas our study classified each fracture according to the AO/OTA system. Fowler and Craig, who also used the AO/OTA system, described a series of 77 patients with diaphyseal fracture and observed differences in fracture types (simple vs. comminuted/spiral) between bisphosphonate users and non-users but did not reach statistical conclusions.[17]

We are aware of only two other case-control studies, both of which studied substantially different populations than ours. Lenart et al.[18] studied Level 1 trauma center patients and compared bisphosphonate use between 41 cases of subtrochanteric/femoral shaft fractures and 82 control patients with intertrochanteric/femoral neck fractures. The authors observed that a significantly greater proportion of patients in the former group were on bisphosphonates as compared to the latter (OR: 4.44, 95% CI: 1.77 to 11.35). As in our study, all fractures were confirmed and classified via radiographs; however, bisphosphonate use was not rigidly defined, and the study compared two populations of patients sustaining different types of fracture rather than those with and without fracture. More recently, Park-Wyllie et al.[19] examined national registry records of women aged 68 or older who were new users of bisphosphonate and compared durations of exposure between those with and without femoral fractures. The authors concluded that women with over 5 years of treatment had an increased risk of diaphyseal fracture (OR: 2.74, 95% CI: 1.25 to 6.02) relative to women with less than 100 days' exposure (OR: 0.76, CI: 0.63 to 0.93). This large primary-care population study provides the best examination to date of fracture risk among bisphosphonate users, but it did not consider fractures among non-users or males and relied on ICD-10 codes for fracture classification. We believe that our case-control study addresses a current gap in the evidence and provides a valuable complement to both these existing case-control studies by comparing risk of diaphyseal fractures among users and non-users of bisphosphonate in a large population. Our findings reinforce the evidence that long-term exposure rather than any exposure to bisphosphonate may be the important risk factor, and that diaphyseal fractures can occur in patients with no exposure.

Our study considered all fractures meeting the major requirements of the ASBMR task report: low-energy, non-comminuted, transverse or short oblique fractures between the lesser trochanter and supracondylar flare. We did not limit analysis to fractures with the specific "minor features" identified by that report (cortical beaking, bilaterality, and cortical thickening) with the rationale that all low-energy diaphyseal fractures are rare, and there is not a proposed mechanism for why bisphosphonate-mediated suppression of bone metabolism would cause only those with the minor features. We did, however, examine the 4 out of 106 cases with all of these minor features. The percentage of bisphosphonate exposure in that subgroup (50%) was higher than that of the entire case cohort (12%) but much smaller than the 96% exposure cited in the 2010 ASBMR report or 77% exposure reported by Lenart et al. Our study therefore confirms the existence of such unique fractures but demonstrates that their occurrence is not restricted to those on long-term bisphosphonate therapy.

The chief limitation of our study was that it was an observational, non-randomized study which can seek to identify an association of exposure with outcome but cannot establish causality. The sources of data were a prospective fracture registry and retrospective electronic health record including prescription orders up to seven years prior to fracture. We have high confidence that all low-energy diaphyseal fractures during the study period were captured but lower confidence in the ability to capture all drug exposures. While we limited inclusion criteria to patients with regular health system encounters, there is potential for missed prescription orders (i.e., patients seeking care elsewhere) and we could not examine exposure prior to 2004 or the long-term bisphosphonate use of >10 years that has been discussed in some prior studies. We addressed concerns about spurious orders by requiring multiple orders over short- and long-term periods and were encouraged to see that these analyses gave similar results. Future studies in this area will likely need to prospectively measure the patient's actual drug exposure and be adequately powered to detect the very low incidence of atypical fractures in a study population.

In conclusion, bisphosphonate exposure was not associated with diaphyseal femur fracture in this case-control study. We propose that the majority of low-energy, geriatric, diaphyseal femur fractures are not associated with bisphosphonate exposure.

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