Are Race and Sex Associated With the Occurrence of Atypical Femoral Fractures?

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Abstract

Background Prior studies have suggested that Asian patients and women may be more likely to sustain atypical femoral fractures in association with bisphosphonate use. However, they do not account for confounders such as asymptomatic patients who are long-term bisphosphonate users or patients sustaining osteoporotic fractures.

Questions/purposes The purpose of this study was to determine the differences in sex and racial association with atypical femoral fractures by comparing demographic characteristics of patients who sustained an atypical bisphosphonate-associated fracture with patients on long-term bisphosphonates without fractures and with patients who sustained osteoporotic fractures.

Each author certifies that he or she, or a member of his or her immediate family, has no funding or commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research* editors and board members are on file with the publication and can be viewed on request. Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Methods Three groups from prospective registries were identified: (1) patients with atypical femur fractures associated with long-term bisphosphonate use (BFF) ($n = 54$); (2) patients on long-term bisphosphonates but with no associated fractures (BNF) ($n = 119$); and (3) patients with osteoporotic proximal femur fractures not associated with bisphosphonates (PFF) ($n = 216$). Age, sex, and self-reported race/ethnicity were documented and compared. Multivariate and univariate analyses were done as well as age- and sex-stratified analyses.

Results Age and sex distributions of the BFF and BNF patients were similar. There was a higher percentage of Asian patients in the BFF group (17%) than in the BNF group (3%; $p = 0.004$) as well as Hispanics (13% versus 3% in BNF; $p = 0.011$). Patients in the BFF group were younger than those in the PFF group (67.5 versus 78.4 years; $p < 0.001$) and had fewer males (7% versus 14%; $p < 0.001$).

Conclusions These data suggest that Asians are at higher risk for atypical bisphosphonate-associated fractures. We recommend closer followup in Asian patients who are taking bisphosphonates.

Level of Evidence Level III, prognostic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

Bisphosphonates are the most frequently used medication for the treatment of osteoporosis because they reduce the incidence of fractures [5, 21]. However, patients who use bisphosphonates over the long term are at risk for atypical femoral fractures [7, 12, 13, 17, 23]. Atypical fractures

differ from osteoporotic fractures in three major ways: origination, mechanism, and radiographic appearance. A bisphosphonate-associated atypical fracture is predominantly subtrochanteric or diaphyseal and is associated with an atraumatic or low-velocity impact [7]. It also has unique radiographic features: transverse or short oblique fractures in the femoral diaphysis with localized lateral periosteal reaction and cortical thickening [18]. These atypical fractures were rarely seen before the introduction of bisphosphonates [10].

A better understanding of the role and interplay of sex and race in the development of bisphosphonate-associated atypical femur fractures is important for management and possible selective monitoring for fracture prevention. Prior reports have demonstrated an association between the race and sex of patients and the incidence of osteoporotic fractures; there are apparent differences in risk factors and treatment outcomes for osteoporotic fractures based on sex, ethnicity, and race [4, 8, 20]. With bisphosphonate use, however, multiple reports of atypical femur fractures in bisphosphonate users have shown that patients tend to be younger, less likely to have diabetes or chronic kidney disease, or to have a prior fragility fracture in the proximal hip, shoulder, wrist, or spine [14]. There are some reports on the racial and ethnic characteristics of the bisphosphonate user who is at risk for atypical fractures. Some studies have reported high percentages of Asians in their patient populations with atypical femoral fractures [9, 14, 15]. Similarly, because it is predominantly women who are diagnosed with osteopenia or osteoporosis and who are treated with bisphosphonates, fewer reports have included sex differences [11, 22]. Despite all these advances, current literature does not help address whether these particular demographic characteristics are associated with confounders such as bisphosphonate users without fractures and patients who sustain osteoporotic fractures or whether they are just a feature of patients with atypical fractures associated with long-term bisphosphonate use.

The purpose of this study was twofold: (1) to determine differences in demographic characteristics (age, sex, and race) between patients with atypical fractures associated with long-term bisphosphonate use and patients on long-term bisphosphonate use but without fracture; and (2) to also determine differences in demographics between patients with atypical fractures associated with long-term bisphosphonate use and patients with osteoporotic proximal femoral fractures who have not taken bisphosphonates.

Materials and Methods

This was an institutional review board-approved, cross-sectional HIPAA-compliant study for which informed

Fig. 1 Radiograph depicting a proximal femur fracture with features indicating an atypical fracture pattern (medial spike; lateral cortical thickening).

consent was waived. We used three different cohorts of patients.

For the first group, a research registry was established from the medical records of patients who met the following inclusion criteria: a history of long-term bisphosphonate use (3 years or more), sustained complete or incomplete atypical femoral fractures (BFF), and treated at our academic medical center between 2004 and 2011. Atypical complete femoral fractures were defined by radiographic evidence of a transverse or short oblique fracture line, medial spike, focal lateral cortical thickening, and relative lack of comminution. Incomplete bisphosphonate-associated atypical femoral fractures were defined by radiographic evidence of focal lateral cortical thickening with or without an incomplete fracture line (Fig. 1). The treating physician evaluated all radiographs. Exclusion criteria were failure to report race/ethnicity, age and duration of bisphosphonate use, and also pathologic fractures and incomplete medical records. Sixty-nine patients with 103 atypical femur fractures met inclusion criteria and 15 were excluded as a result of missing data resulting in a total of 54 who were selected as part of this cohort. The second group consisted of patients on long-term bisphosphonate use (3 years or more) but without associated fractures (BNF) who were enrolled between 2009 and 2012

from an independent registry. This registry was maintained by our medical endocrinology group and included all patients being treated in that practice who returned for followup and consented to participate in the study, which involved close followup with radiographs. One hundred forty-one patients were identified and 22 patients were excluded as a result of incomplete data leaving a total of 119. The third group consisted of 219 patients with typical osteoporotic proximal femur fractures (intertrochanteric or subtrochanteric) who did not report bisphosphonate use (PFF) and were enrolled between 2011 and 2012; three patients were excluded as a result of incomplete data leaving a total of 216. This final group was a database of all patients who underwent surgery at our institution for an osteoporotic hip fracture over the enrollment period; there were no exclusion criteria except for incomplete records.

Patients' age, sex, and race/ethnicity were documented from their medical records by trained research personnel. Races were grouped into five categories: white, black, Hispanic, Asian, and "other" racial/ethnic groups (South Asian or Indian, Arab, and Persian groups were included in "other"). These were also compared with the demographic differences in our geographic area based on latest available census data. Sex and age stratification was carried out to further isolate confounders.

Basic descriptive statistical analyses were used to describe the patient population. Multivariate analysis of numerical variables was carried first using a multivariate analysis of variance to compare all three groups followed by post hoc univariate tests using the Mann-Whitney U test to determine direct differences between two groups. Fisher's exact test or chi-square test was used for nominal variables as appropriate. Odds ratios were obtained with 95% confidence intervals for each individual race/ethnicity group versus the sum of all other groups. Statistical significance was defined as $p \leq 0.05$. Values are reported as mean $\pm$ SDs or percentages.

Results

Asian and Hispanic patients were represented in a greater proportion in the BFF group as compared with the BNF group. Mean age and sex distribution was similar among bisphosphonate users (BFF and BNF) as well as mean time of bisphosphonate use (Table 1). The most notable variation among group compositions was seen among white and Asian patient groups. Almost 17% of the BFF group was composed of Asians, whereas the remainder was mostly white (57%). The proportion of BFF Asians was significantly higher than those found in the BNF group (3%; $p = 0.004$). Also notable, the proportion of Hispanics in the BNF group (3%) was significantly less than that found in

the BFF group (13%; $p = 0.011$) (Table 1). Although the specific composition of the "other" category was not analyzed, a significantly greater number of BFF patients were classified into this group (7%) as compared with the BNF patients (1%; $p = 0.033$). After conducting an odds ratio (OR) analysis, we found that a patient who is of Asian descent is more likely to have sustained an atypical femoral fracture (BFF) after long-term bisphosphonate use than a patient of any other race (OR, 5.8; 95% confidence interval [CI], 1.69–19.62); Hispanics also were more likely to have an atypical fracture (OR, 5.8; 95% CI, 1.43–23.22). Whites were less likely to sustain an atypical femoral fracture (BFF) than all other races combined (OR, 0.2; 95% CI, 0.07–0.34). There was a relatively small difference among blacks, denoting a higher risk (OR, 1.7; 95% CI, 0.37–7.83). Interestingly, "other" races denoted the highest odds (OR, 9.4; 95% CI, 1.03–86.58) although the confidence interval was significantly wide. Asians in the BFF group had a mean of 10.44 (± 4.59) years of bisphosphonate consumption, whereas those in the BNF group had a mean of 7.75 (± 3.59) years; however, this difference was not significant ($p = 0.323$). Because the incidence of atypical fractures rises with prolonged bisphosphonate therapy, we compared the duration of bisphosphonate use between the Asian population of the BFF and BNF groups and found that although the BNF group had a higher average consumption time, this difference was not statistically significant. To assess if age and sex played a major role in the variation of race proportions as confounders, we sought to compare race distribution among age-stratified groups and each sex separately. In the BFF and BNF groups, all males ($n = 3$ and $n = 9$, respectively) were white and no other races were represented; hence, no statistical analysis was possible. Among women ($n = 199$), no significant differences were found between BFF ($n = 51$) and BNF ($n = 148$) (Table 2). Similarly, when stratification was done, the numbers of each of the BFF age subgroups were significantly reduced; hence, statistical analyses were considerably hindered (Table 3). Still, some significant differences were found between BFF and BNF in the percentage of whites who were younger than 59 years old (33% versus 93%, respectively; $p = 0.003$) and between 70 and 79 years of age (53% versus 92%; $p = 0.003$). The proportion of Hispanics was also significantly different between BFF and BNF among patients aged 70 to 79 years (23% versus 2%; $p = 0.021$). We further analyzed if any particular race had a significantly higher incidence of bilateral atypical fractures; however, no significant differences could be found. The only significant difference we found was among the "others" race group in which patients who sustained bilateral fractures had significantly longer times of bisphosphonate therapy than those who did not (9.33 ± 1.16 years versus 2.50 ± 0.50 years; $p = 0.005$).

Table 1. Patient information

Patient variables	BFF	BNF	95% CI	p value	PFF	95% CI	p value
Age (mean years) (SD)	67.5 (9.6)	70.4 (9.5)	−5.9 to 0.2	0.128	78.4 (13.9)	−14.8 to −6.9	< 0.001
Male (number) (%)	3 (6)	7 (6)	–	1.000	58 (27)	–	< 0.001
Female (number) (%)	51 (94)	112 (94)	–		158 (73)	–	
White (number) (%)	31 (57)	107 (90)	–	< 0.001	166 (77)	–	0.004
Black (number) (%)	3 (6)	4 (3)	–	0.679	17 (8)	–	0.405
Hispanic (number) (%)	7 (13)	3 (3)	–	0.011	20 (9)	–	0.279
Asian (number) (%)	9 (17)	4 (3)	–	0.004	6 (3)	–	0.001
Other (number) (%)	4 (7)	1 (1)	–	0.033	7 (3)	–	0.157
Duration of bisphosphonate use (mean years) (SD)	8.69 (3.8)	7.94 (2.9)	−0.3 to 1.8	0.355	N/A	N/A	N/A

Bold type is statistically significant ($p < 0.05$); BFF = bisphosphonate-associated femur fractures; BNF = bisphosphonate users with no fractures; PFF = osteoporotic proximal femur fractures not associated with bisphosphonates; CI = confidence interval.

Table 2. Age, race distribution, and duration of bisphosphonate use among women

Patient variables	BFF	BNF	p value	PFF	p value
Age (mean years) (SD)	67.24 (9.60)	70.13 (9.39)	0.134	80.45 (11.68)	< 0.001
White (number) (%)	28 (55)	100 (89)	< 0.001	121 (77)	0.004
Black (number) (%)	3 (6)	4 (7)	0.679	9 (6)	1.000
Hispanic (number) (%)	7 (14)	3 (3)	0.011	15 (10)	0.433
Asian (number) (%)	9 (18)	4 (4)	0.004	6 (4)	0.002
Other (number) (%)	4 (8)	1 (1)	0.034	7 (4)	0.469
Duration of bisphosphonate use (mean) (SD)	8.84 (3.84)	7.99 (2.97)	0.268	N/A	–

Bold type is statistically significant ($p < 0.05$); BFF = bisphosphonate-associated femur fractures; BNF = bisphosphonate users with no fractures; PFF = osteoporotic proximal femur fractures not associated with bisphosphonates; N/A = not applicable.

When compared with the PFF group, the BFF patients had a higher proportion of Asians, higher proportion of women, and a lower mean age. Patients in the PFF group tended to be older than those in the BFF group (78.4 versus 67.5 years, respectively; $p < 0.001$) and had a significantly higher proportion of male patients (26.9% versus 5.6%, respectively; $p < 0.001$). The proportion of BFF Asians was also significantly higher than those found in the PFF group (2.8%; $p = 0.001$). Like the previous comparison, the proportion of whites in the BFF group was also reduced as compared with the PFF group (76.9%; $p = 0.004$). When comparing atypical femur fractures and proximal femur fractures (typical), the results of the OR analysis show that a patient who is of Asian descent is also more likely to have sustained an atypical femoral fracture than all other races combined (OR, 7; 95% CI, 2.37–20.65). Hispanics also were more likely to have an atypical fracture (OR, 1.4; 95% CI, 0.58–3.65). Similarly, whites were less likely to sustain an atypical femoral fracture than all other races combined (OR, 0.4; 95% CI, 0.22–0.76) as well as blacks (OR, 0.7; 95% CI, 0.19–2.44). “Other” races also demonstrated high odds (OR, 2.4; 95% CI, 0.67–8.48). To assess if age and sex played a major role in the variation of

race proportions as confounders, we sought to compare race distribution among age-stratified groups and each sex separately. As stated previously, in the BFF groups, all males ($n = 3$) were white and no significance was obtained. Among women ($n = 209$), the BFF group ($n = 51$) had a higher percentage of whites than the PFF group ($n = 158$; $p = 0.004$) (Table 2). When analyzing the age stratification, although the reduced numbers of the BFF age subgroups hindered the statistical analyses, the most notable significant differences found between BFF and PFF were in the distribution of the subgroups (Table 3). The distribution of the BFF subgroup inclined toward younger ages, whereas the distribution of the PFF was toward older ages. Other significances detected were the percentages of Asians in patients younger than 59 years, which were higher in the BFF group (Table 3).

Discussion

The role of sex and race differences in the development of bisphosphonate-associated atypical femur fractures is important to understand. The association of demographics

Table 3. Age-stratified sex distribution, race distribution, and duration of bisphosphonate use

Patient variables per age		BFF	BNF	p value	PFF	p value
≤ 59 years		n = 12 (22%)	n = 14 (11%)	0.106	n = 22 (10%)	0.023
Sex	Male	0	0	–	15 (68%)	< 0.001
Number (%)	Female	12 (100%)	14 (100%)		7 (32%)	
Race/ethnicity	White	4 (33%)	13 (92.9%)	0.003	10 (46%)	0.717
Number (%)	Black	3 (25%)	0	0.085	5 (23%)	1
	Hispanic	2 (17%)	0	0.203	6 (27%)	0.681
	Asian	3 (25%)	1 (7.1%)	0.306	0	0.037
	Other	0	0	–	1 (4%)	1
Duration of bisphosphonate use (years) (mean)		8.25	6.57	0.467	N/A	–
60–69 years		n = 19 (35%)	n = 42 (36%)	1	n = 19 (9%)	< 0.001
Sex	Male	2 (11%)	2 (5%)	0.582	2 (11%)	1
Number (%)	Female	17 (89%)	40 (95%)		17 (89%)	
Race/ethnicity	White	13 (68%)	36 (86%)	0.165	16 (84%)	0.447
Number (%)	Black	0	3 (7%)	0.545	2 (11%)	0.486
	Hispanic	1 (5%)	2 (5%)	1	1 (5%)	1
	Asian	3 (16%)	1 (2%)	0.085	0	0.23
	Other	2 (11%)	0	0.093	0	0.486
Duration of bisphosphonate use (years) (mean)		7.74	7.74	0.771	N/A	–
70–79 years		n = 17 (32%)	n = 42 (36%)	0.73	n = 52 (24%)	0.296
Sex	Male	0	3 (7%)	0.55	18 (35%)	0.003
Number (%)	Female	17 (100%)	39 (93%)		34 (65%)	
Race/ethnicity	White	9 (53%)	38 (92%)	0.003	42 (81%)	0.053
Number (%)	Black	0	1 (2%)	1	3 (6%)	0.57
	Hispanic	4 (23%)	1 (2%)	0.021	4 (7%)	0.096
	Asian	2 (12%)	1 (2%)	0.197	2 (4%)	0.252
	Other	2 (12%)	1 (2%)	0.197	1 (2%)	0.148
Duration of bisphosphonate use (years) (mean)		10.24	8.25	0.094	N/A	–
80–89 years		n = 4 (7%)	n = 17 (14%)	0.314	n = 85 (39%)	< 0.001
Sex	Male	1 (25%)	1 (6%)	0.352	14 (18%)	0.554
Number (%)	Female	3 (75%)	16 (94%)		70 (82%)	
Race/ethnicity	White	3 (75%)	16 (94%)	0.352	65 (77%)	1
Number (%)	Black	0	0	–	4 (5%)	1
	Hispanic	0	0	–	8 (9.4%)	1
	Asian	1 (25%)	1 (6%)	0.352	4 (5%)	0.21
	Other	0	0	–	4 (5%)	1
Duration of bisphosphonate use (years) (mean)		8.75	8.32	0.891	N/A	–
≥ 90 years		n = 2 (4%)	n = 4 (3%)	1	n = 38 (18%)	0.009
Sex	Male	0	1 (25%)	1	8 (21%)	1
Number (%)	Female	2 (100%)	3 (75%)		30 (79%)	
Race/ethnicity	White	2 (100%)	4 (100%)	–	33 (87%)	1

Table 3. continued

≥ 90 years		n = 2 (4%)	n = 4 (3%)	1	n = 38 (18%)	0.009
Number (%)	Black	0	0	–	3 (8%)	1
	Hispanic	0	0	–	1 (3%)	1
	Asian	0	0	–	0	–
	Other	0	0	–	1 (3%)	1
Duration of bisphosphonate use (years) (mean)		7	10	0.24	N/A	–

Bold type is statistically significant; N/A = not applicable.

(ie, race and age) to bisphosphonate-associated fractures has been documented by other studies but they do not address whether these particular demographic characteristics are associated with occurrence or higher incidence of atypical femoral fractures in particular groups. The purpose of this study was to determine the differences in the sex and racial association with atypical femoral fractures by comparing demographic characteristics of patients who sustained an atypical bisphosphonate-associated fracture with patients on long-term bisphosphonates without fractures and with patients who sustained osteoporotic fractures.

This study had a number of limitations. First, there are confounding variables that could have influenced our results to a certain extent such as the interplay of demographics with each other (ie, age and sex). To address this, after analyzing overall data, we stratified our data by age and sex to reduce the influence of these variables. By stratifying data, the resulting numbers in each subgroup were further reduced, and the BFF subgroups' results were too small that perhaps statistical significance was difficult to achieve. Other confounders such as the influence of other drugs (ie, proton pump inhibitors and glucocorticoids) were not addressed in this study and could possibly have an influence on our results. Recently, hypocalcemia resulting from latent hypoparathyroidism, obesity, early menopause, and bone mineral density was detected because further risk factors may also influence the development of atypical femur fractures. These risk factors, as an addition to use of the previously mentioned drugs, could be addressed in future studies to further describe these fractures. Second, we used three different registries to compare the patients and this may have introduced selection bias; however, all three were from our institution and because they encompassed the same catchment area, we feel they represented the same population group allowing us to conduct the comparison. Another confounder deals with the diversity of the population served by our institution. We compared our results with the proportions from this population given from the US Census to determine if the

representation of the different races was a product of such diversity or a true characteristic of each group.

We found a greater proportion of Asians, Hispanics, and those included within the “other” (namely south Asians) category in the BFF group and hence a lower proportion of whites as compared with asymptomatic bisphosphonate users. A previous study evaluating patients with atypical femoral fractures from the Kaiser Permanente Northern California cohort found that the largest group was Asians at 49.3% [9]. Another study showed that although the majority of patients were white (72%), a significant percentage of Asian patients (24%) sustained this fracture [15]. Although the percentages of Asians identified were drastically different, each author has argued that their findings were likely attributable to the significant Asian populations at their institutions [9, 15]. Hence, the differences in racial compositions presented in these studies [9, 15] may be explained by the diversity of the populations unique to the sites where the subjects were selected. To put our results into context, according to data from the 2010 US Census, Asians constitute approximately 12.7% of the population in New York City, which represents the population that our institutions serves; Hispanics account for 28.6% [1]. Although the higher proportion of Asians has been already reported, a finding of a significantly lower proportion of Hispanics among patients with asymptomatic long-term bisphosphonate use (2.5%) has yet to be reported in the literature. The patients on long-term bisphosphonates (both those who were asymptomatic and others who sustained atypical fractures) had similar age and sex distributions. This is expected because postmenopausal women are more likely to have osteoporosis and been treated with bisphosphonates [4].

We also found a greater proportion of Asians in patients with atypical fractures as compared with other femur fractures. Interestingly, also age and sex distributions were different and these results were maintained when analyzing sex- and age-stratified data, suggesting that these demographic characteristics are independent of each other and associated with the BFF group. Patients with atypical

fractures were younger and had fewer males. Another study using the same Kaiser Permanente Northern California cohort mentioned previously found that the proportion of Asian women with atypical fractures (50%) represents a 20-fold higher proportion compared with those with non-atypical fractures (2.4%) and compared with 12% in their general Northern California cohort [14]. This number is much greater than what we found (16.7%), which represents only a 5.9-fold higher proportion compared with the PFF group. Although this study included South Asians (2.50%), Filipino (10.5%), and other Asians (5.3%) in their total “Asian” classification, we included these populations in the “other” category (10.6%), showing distinctly greater proportions of minorities who may be inadequately defined by such a broad categorization [14]. Another study has identified Asian women (Japanese) as having features that may contribute to lower rates of typical proximal femur fractures such as differences in hip axis; however, these femoral biomechanical differences may contribute to risk of atypical femur fracture [16]. Our proportions of BFF Hispanics (12.1%) and PFF Hispanics (9.3%) are somewhat similar to a report published by Dell et al. in which there were 8.5% of Hispanics [9]. Given the similarities between our BFF and PFF percentages, it is difficult to draw any particular conclusions. However, it is possible that Hispanics are at relatively greater risk for both osteoporosis-related fractures (PFF) as well as bisphosphonate-associated atypical fractures (BFF). Patients at risk for osteoporotic fractures should not be discouraged from initiating the use of bisphosphonates. Several other studies have shown that the risk of atypical fractures associated with bisphosphonate use is small as compared with the overall benefits of this form of pharmacotherapy [2, 3, 6, 19].

Our study suggests that patients who sustain bisphosphonate-related atypical femur fractures have a distinctly different demographic composition as compared with those using bisphosphonates but who do not sustain fractures and with those who sustain osteoporosis-related proximal femur fractures. We found that these patients tended to be younger and most likely women of Asian descent leading us to suggest that further studies should include greater consideration of patient demographic characteristics to determine adequate medical management of patients with atypical fractures. We hope that further studies will determine whether sex and different racial characteristics can be identified as risk factors for bisphosphonate-associated fractures as well as if differences in femur geometry, bone metabolism, nutritional factors, and pharmacologic exposures between race/ethnic groups convey higher risks and potentially minimize or prevent this complication.

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