

Statement of Purpose

- The purpose of this study was to determine the demographic risk profile for metatarsal fracture in women receiving bisphosphonate (BP) therapy.
- Is the demographic risk profile similar to atypical femur fracture? Is metatarsal fracture associated with BP use and/or atypical fracture?

Introduction

- Bisphosphonate (BP) drugs are highly effective in reducing osteoporotic fracture risk in older women.¹
- Rare atypical femur fractures are associated with long-term BP use, due to reduced bone remodeling and microdamage repair.²
- Increased metatarsal fractures among women with atypical femur fracture have been reported.^{3,4}
- Up to 50% of atypical femur fracture cases occur in Asians, a race with low risk of typical femur fracture.⁵

Methods

- Setting: Kaiser Permanente Northern California
- Cohort: 48,390 women age ≥ 50y who initiated oral BP in 2002-2007 (3+ years follow-up)
- Hospital, ED, urgent care, orthopedic, and podiatry visit diagnoses of closed metatarsal fracture (ICD-9 825.25) or metatarsal stress fracture (733.94) were identified after the BP initiation date
- Radiology reports were reviewed for adjudication of metatarsal fracture

Methods

Table 1. Metatarsal Fracture Adjudication and Assignment

Fracture Status	Findings	Assignment
Fracture Confirmed	Lucency, periosteal reaction, cortical disruption, irregularity, sub/acute, healing fracture	Assigned as "fracture"
Fracture Equivocal	Report suggests fracture but radiographic findings not specifically noted	Assigned as "fracture"
No Fracture or Uncertain	No imaging study obtained or radiology and/or clinical records were unavailable	Assigned as "no fracture"

Clinical notes were reviewed if radiology report was unavailable, no fracture was noted, or fracture was reported as healed or old

STATISTICAL ANALYSES

- Chi-square (or Fisher exact) test and Student's T-test were used to compare differences between subgroups.
- Cox proportional hazard analyses were used to examine the association between metatarsal fracture and race, clinical risk factors, and BP treatment.

Results

- Of 48,390 women who initiated oral BP:
 - 1204 (2.5%) had a coded diagnosis of metatarsal fracture after BP initiation (excluding first 6 months).
 - 1123 (2.3%) were classified as metatarsal fracture
 - 1055 acute or healing fractures
 - 68 equivocal fractures
 - 81 were not classified as metatarsal fracture
 - 74 likely not fractures (no imaging or by report)
 - 7 had no records available
- Among 1123 with a metatarsal fracture, 61% had a 5th metatarsal fracture; 30% were <65y at time of fracture

Results

Table 2. Baseline Characteristics of Women by Fracture Status

	Metatarsal Fracture	No Metatarsal Fracture
Age at entry:		
45-64	511 (46%)*	16,568 (35%)
65-79	455 (41%)	22,556 (48%)
80+	157 (14%)	8143 (17%)
Race group:		
White	816 (73%)*	30,785 (65%)
Asian	125 (11%)	8147 (17%)
Other	182 (16%)	8335 (18%)
Prior fracture	344 (31%)*	11,895 (25%)
Diabetes mellitus (DM)	110 (10%)*	3628 (8%)
Rheumatoid arthritis (RA)	56 (5%)*	1662 (4%)
Glucocorticoids (GC)	57 (5%)*	1628 (3%)

*Women with metatarsal fracture were younger, more likely to be of white race, have prior fracture, DM, RA and receive GC. * p <0.05*

Table 3. Association of Race and Risk of Metatarsal Fracture

	Metatarsal Fracture Incidence per 100,000	Metatarsal Fracture (Hazard Ratio)* Adjusted for age + risk factors	Metatarsal Fracture (Hazard Ratio)* Adjusted for age + risk factors + BP exposure
ALL	312		
By Race:			
White	349	Referent	Referent
Asian	197	0.53 (0.44-0.65)	0.51 (0.42-0.63)
Other	291	0.82 (0.69-0.97)	0.81 (0.68-0.96)

Adjusting for age, clinical risk factors, and BP use, Asian race was associated with 50% lower risk of metatarsal fracture vs. white.

- *In these same analyses, current BP use [HR 1.80 (1.54-2.10)] was associated with a greater risk of metatarsal fracture but the duration of prior BP use [HR 0.99 (0.97-0.997)] was not.*

Results

Table 4. Metatarsal & Atypical Femur Fracture during Follow-Up

	Metatarsal Fracture	No Metatarsal Fracture
Atypical Fracture	2.9%	97.1%
No Atypical Fracture	2.3%	97.7%

The association between metatarsal fracture and atypical femur fracture was not significant (p=0.7) in this cohort, but the number of women with atypical femur fracture was extremely small (0.1%).

Conclusion

- Among women who received BP, the risk of metatarsal fracture was higher with younger age, white race, prior fracture, diabetes, rheumatoid arthritis and glucocorticoid therapy. This is consistent with the demographic risk profile of osteoporotic fracture and not atypical fracture.
- The majority of metatarsal fractures that occurred in these women were isolated to the 5th metatarsal.
- While current BP use was associated with higher risk of metatarsal fracture, the duration of prior BP use was not.
- Overall, metatarsal fracture risk did not appear to be associated with longer BP use or atypical femur fracture, but the subset of metatarsal stress fractures (excluding traumatic fracture) was not specifically examined.

References

1. Favus MJ. Bisphosphonates for osteoporosis. *N Engl J Med.* 2010;363(21):2027-2035.
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3. Armamento-Villareal R, et al. Bone turnover in bone biopsies of patients with low energy cortical fractures receiving bisphosphonates: a case series. *Calcif Tiss Int.* 2009; 1:37-44
4. Waterman GN, et al. Metatarsal stress fractures in patients with multiple myeloma treated with long-term bisphosphonates: a report of 6 cases. *J Bone Joint Surg Am.* 2011; 93(18),e106
5. Lo J, et al. The association of race/ethnicity and risk of atypical femur fracture among older women receiving oral bisphosphonate therapy. *Bone.* 2016; 85:142-147.