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SHORT COMMUNICATION

Atypical femur fracture incidence in women increases with duration of bisphosphonate exposure

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Abstract

Summary In a northern California population of older women who were treated with oral bisphosphonate drugs, the incidence of atypical femur fracture, a rare complication of treatment, increased with longer duration of bisphosphonate exposure. These findings align with those previously reported in an independent southern California population.

Introduction The age-adjusted incidence of atypical femur fracture (AFF) reported in southern California increased with bisphosphonate (BP) exposure, ranging up to 113 per 100,000 person-years for 8–10-year exposure. This study examines the incidence of AFF in a northern California population.

Methods Women age 45–89 years who initiated oral BP during 2002–2014 in Kaiser Permanente Northern California were followed for AFF outcome, defined by a primarily transverse diaphyseal femur fracture through both cortices, with focal periosteal/endosteal hypertrophy, minimal trauma, and minimal/no comminution. Total BP exposure was determined from dispensed prescriptions. The incidence of AFF, calculated for 2-year BP categories ranging from < 2 to > 10 years, was age-adjusted using the 2000 US Census.

Results Among 94,542 women, 107 experienced an AFF during or < 1 year after BP cessation (mean exposure 6.6 ± 3.0 years and total days' supply 5.7 ± 2.8 years at AFF). A strong relationship between AFF incidence and increasing BP exposure was seen, more than doubling for each 2-year category until 8–10 years. Among women with 2- to < 4-year BP, the crude and age-adjusted incidence was 18 and 9 per 100,000 person-years but increased over 2- and 5-fold for women with 4- to < 6- and 6- to < 8-year BP, respectively. For those receiving ≥ 8-year BP, the crude and age-adjusted incidence peaked at 196 and 112 per 100,000 person-years exposure.

Conclusion Incidence of AFF increases markedly after 4–6 years of BP. These trends align with southern California and confirm a strong BP duration-related risk of this rare but serious event.

Keywords Atypical femur fracture · Incidence · Bisphosphonate

Introduction

Atypical femur fractures (AFF) in women with bisphosphonate (BP) exposure were first reported in 2005 [1]. The American Society for Bone and Mineral Research (ASBMR) task force identified over 300 AFF cases from more than 30 reports during 2006–2010, including 286 cases receiving BP treatment for osteoporosis [2]. Although causality was not established and 19 AFFs occurred in BP-naïve individuals, the median treatment duration among BP-exposed cases was 7 years [2]. In 2012, Dell and colleagues estimated the magnitude of the association between BP duration and AFF [3], using data from Kaiser Permanente Southern California (KPSC) members identified from a system-wide program during 2007–2011, for whom BP exposure was characterized using prescriptions dispensed in 1996–2011. Based on incident AFF events in 2007–2011, they observed a marked increase in the age-adjusted rate of AFF from 1.8 to 113 per 100,000 person-years BP exposure, comparing those with < 2- versus 8–10-year BP exposure. While this study was limited by lack of AFF ascertainment during the

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entire period of BP exposure, the findings represented the largest and most comprehensive evidence to date of the association between BP duration and risk of AFF.

In the current study, we aimed to replicate and strengthen these prior analyses using a Northern California population where hospitalization, pharmacy, and radiologic data were similarly centralized within an integrated healthcare system. Two key advancements in our design were tracking of AFF events from the point of BP initiation and having available radiologic images for up to 14 years rather than just the last 5 years of observation. This allowed a more precise examination of how AFF incidence varies with incremental BP exposure from < 2 to > 10 years.

Methods

Setting and study population

Kaiser Permanente Northern California (KPNC) is a large, integrated healthcare delivery system serving > 4,000,000 members. Electronic databases pertaining to hospitalization, ambulatory care, pharmacy, and membership records are available since 1995. Digital radiologic images are centralized, beginning in 2002 and across all KPNC imaging centers by 2005.

The study population included KPNC female members aged 45–89 years who newly initiated oral BP drugs (with no BP at least 2 years prior to index) between 2002 and 2014. The BP users included those who received oral alendronate, risedronate, or ibandronate and excluded those who received intravenous BP (zoledronic acid, pamidronate, or ibandronate). Also excluded were women without continuous health plan membership for 2 years prior to BP initiation (allowing ≤ 3-month gaps) and those with diagnoses of (secondary) metastatic cancer beyond lymph nodes (International Classification of Diseases, 9th Revision; ICD-9 197.x-199.0), multiple myeloma (ICD-9 203.0x), Paget's disease of bone (ICD-9 731.0), osteogenesis imperfecta (ICD-9 756.51), hypophosphatasia (ICD-9 275.3), or primary hyperparathyroidism (ICD-9 252.01); receipt of teriparatide or denosumab; estimated glomerular filtration rate < 30 mL/min/1.73 m^2 calculated from outpatient serum creatinine level [4]; or receipt of peritoneal/hemodialysis or renal transplantation. Women were followed through September 30, 2015, or until an exclusion criterion was met, age > 89 years, membership disenrollment, or death, whichever was first. The study was approved by the KPNC Institutional Review Board, and the requirement for informed consent was waived due to the nature of the study. Findings for a cohort subset were previously reported in analyses examining race/ethnicity and AFF risk [5].

Bisphosphonate exposure

Bisphosphonate prescriptions were quantitated based on dispensed days' supply. Stock pilling of medication was allowed when prescriptions overlapped ≤ 30 days. For the occasional situation of substantial prescription overlap (where prescriptions overlapped > 30 days), the second prescription took precedence and contributed BP days' supply during the overlap period [6]. The total BP exposure period was determined by the time spanning the first and last prescriptions during follow-up, inclusive of all treatment gaps. We also assessed the total BP days' supply within the total BP exposure period.

Atypical femur fracture classification

To identify AFFs, we examined radiologic images linked to hospitalizations for principal diagnoses of subtrochanter (ICD-9 820.22, 820.32) and femoral shaft (ICD-9 821.0x, 821.1x) fractures, pathologic fracture of femur but not femoral neck (ICD-9 733.15), femur stress fractures (ICD-9 733.97), and principal diagnoses of pertrochanter fracture (ICD-9 820.20, 820.21) when combined with an above secondary diagnosis code (ICD-9 820.22, 820.32, 821.0x, 821.1x, 733.15, 733.97) and radiology reports localizing fracture to the femoral diaphysis. Only 17 had coded diaphyseal fractures without available radiographs, of whom 15 were classified as femoral neck, pertrochanter, distal femur, or periprosthetic fracture by radiology reports. Radiologic images were examined for anatomic localization, with subtrochanteric fracture defined by location ≤ 5 cm below the lower border of the lesser trochanter (Orthopedic Trauma Association criteria) [7, 8] and femoral shaft fracture defined by location distal to this region and up to but not including the distal metaphyseal flare [5, 9]. Due to the heterogeneity of existing subtrochanteric fracture classification systems [7], radiologic image review is required to identify diaphyseal fractures; our previous study found that only one-fourth of subtrochanteric-coded fractures localized to the subtrochanter [9]. We also found that up to one-third of femoral shaft-coded fractures were periprosthetic [10].

Focusing on those with complete diaphyseal femur fractures, AFF adjudication was based on 2013 ASBMR major criteria: (1) minimal or no trauma, (2) minimal or no comminution, (3) transverse fracture (with or without medial spike), (4) localized periosteal or endosteal thickening at the lateral cortex of the fracture site, and (5) complete fracture requiring extension through both cortices [11] (partial AFF criteria not applicable). Precipitating cause was identified, including spontaneous cases (occurring with twisting or non-traumatic lateral impact) and those from minor trauma/fall.

Demographic and clinical characteristics

For women followed for potential AFF (denominator), patient age was determined at the midpoint of each 2-year BP exposure interval. Among AFF cases, age at fracture was also determined. Self-reported race/ethnicity was ascertained from health plan databases.

Statistical analyses

To examine the incidence of AFF by person-years BP exposure, the number of AFF cases (first complete AFF per woman) was divided by the total person-years in each successive 2-year BP exposure category up to a maximum of 13.75 years. Each woman continuing BP was moved into the next exposure category, contributing person-years BP exposure within that interval until AFF outcome or exclusion criteria met, whichever came first. The incidence of AFF was calculated for each 2-year BP exposure category (with 95% confidence intervals) and included AFF events occurring < 1 year following BP cessation. We also calculated age-adjusted incidence using weights derived from the 2000 US Census for women age 45–89 (5-year age groups) [12] to allow comparison of age-standardized rates of AFF. Analyses were conducted using SAS statistical software (version 9.4, Cary, NC).

Results

Among 94,542 women who received BP (66.7% white non-Hispanic, 17.2% Asian, 16.1% all other or unknown race/ethnicity), the average (± SD) age at treatment initiation was 69.9 ± 10.0 years. During follow-up, the median BP exposure period was 2.2 years (interquartile range, IQR 0.5–5.0), including median days' supply 1.3 years (IQR 0.4–3.3). Among 49,205 women who received BP > 2 years, the median BP exposure was 4.8 years (IQR 3.2–7.3), and two-thirds of this period was covered by days' supply of the drug (median 3.2, IQR 2.0–5.0 years). Table 1 shows the number of women, their age, and person-exposure time by successive BP duration category.

Among 94,542 women who initiated BP, 113 experienced an AFF during follow-up (52.2% subtrochanter, 47.8% femoral shaft). The majority with AFF were Asian (62.8%), followed by non-Hispanic white (26.6%) race. The mean (± SD) age at AFF was 74.1 ± 7.8 years. Notably, 22% of AFF cases occurred with minimal or no trauma (twisting or minimal impact), while 78% were related to minor trauma/fall. A substantial proportion (38%) had contralateral femur findings before or following AFF; these included complete AFF or report of "transverse" fracture (13%), incomplete AFF with prophylactic intramedullary rod placement (5%), and scintigraphic stress fracture or linear lucency (1%), while the remainder showed only focal periosteal or endosteal thickening in the lateral cortex (19%).

Table 1 Number of women, age, person-years of treatment, and the incidence of atypical femur fracture (AFF) by bisphosphonate (BP) exposure category

BP exposure category (years)	Women *N*	Age, years mean ± SD	Person-years per category	Crude incidence of AFF per 100,000 person-years (95% confidence interval)
< 2	94,542	70.9 ± 9.9	129,528	6 (3–12)
2 to < 4	49,205	71.8 ± 9.4	78,415	18 (10–30)
4 to < 6	30,626	72.9 ± 9.0	47,347	42 (26–65)
6 to < 8	17,732	74.2 ± 8.5	26,810	93 (60–138)
8 to < 10	9665	75.5 ± 8.2	13,774	196 (129–285)
≥ 10	4573	76.7 ± 7.8	6686	194 (104–332)

For these 113 incident AFF events, 107 occurred during the period spanning BP exposure or < 1 year after BP cessation, including 6 cases that occurred 6–10 months after BP cessation. Thus, 107 AFF cases (mean total exposure 6.6 ± 3.0 years and total days' supply 5.7 ± 2.8 years at the time of fracture) were used to calculate the incidence of AFF per interval of BP exposure, expressed in person-years. There were 22 AFF cases with BP exposure < 4 years, compared with 85 cases with BP exposure ≥ 4 years. The remaining six AFF events occurring 1 to 3.5 years after BP cessation were not included as outcomes.

Table 1 shows the incidence of AFF per 100,000 person-years BP exposure for each successive 2-year category. By 8- to < 10-year BP, the incidence increased to 196 per 100,000 person-years. Figure 1 shows both crude and age-adjusted incidences of AFF by BP category, the latter standardized to the 2000 US Census to allow comparison of findings. We observed a strong association of AFF incidence with increasing BP exposure, more than double for each successive 2-year BP category until > 10 years. Among women with 2- to < 4-year BP, the crude and age-adjusted incidences were low at 18 and 9 per 100,000 person-years, respectively, but increased over two- and five-fold for those with 4- to < 6- and 6- to < 8-year BP exposure. For those receiving ≥ 8 years of BP, the crude and age-adjusted incidences peaked at 196 and 112 per 100,000 person-years exposure, respectively.

Discussion

These findings of a very strong relationship between duration of BP and AFF risk in northern California are aligned with trends reported in southern California [3]. In designing the study, we used a similar approach to examine the incidence, with similar exposure criteria (BP) and outcome (AFF). Our goal was to replicate KPSC's approach, adjusting

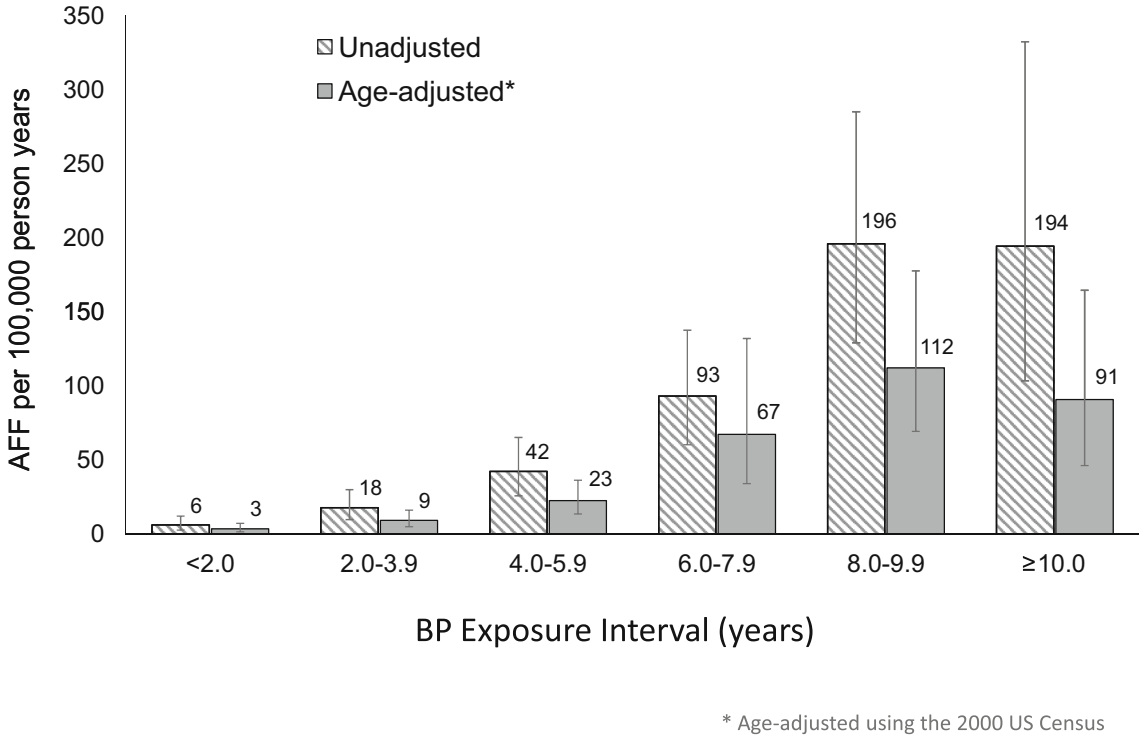

Fig. 1 Incidence of atypical femur fracture (AFF) by bisphosphonate (BP) exposure category (error bars represent 95% confidence intervals)

methodology based on added data capacity and perceived needs to clarify results or address prior methodologic limitations. Our longer period of AFF ascertainment (the entire BP observation period for each woman) contributes to more comprehensive AFF capture, although the KPSC study also included partial/incomplete AFF. Both studies required all five ASBMR major criteria for AFF, including periosteal/endosteal thickening. Thus, our incidence rates are conservative, because the ASBMR definition requires only 4 of 5 criteria [11]. The current study builds on prior KPNC analyses [5] and extends the number of BP users and AFF case catchment by nearly 2-fold. A finding of interest for both KP California regions is that at least half of the AFF cases occurred in Asian women [3, 5].

The KPSC's Healthy Bones Program identified 1.8 million individuals age ≥ 45 years with ≥ 6 months' health plan membership during a 5-year period 2007–2011, of whom 188,814 had pharmacy records indicating ≥ 1 oral BP prescription received in 1996–2011 [3]. The KPSC AFFs were identified only if they occurred during 2007–2011, when radiologic images were available. Both KPNC and KPSC studies examined the risk of AFF with incremental BP exposure. For KPNC, each subject was observed in successive 2-year BP duration categories until (1) AFF, (2) BP cessation, (3) exclusion criteria met, or (4) end of follow-up. Thus, age of the remaining KPNC cohort increased with BP duration. The 2000 US Census was used to calculate age-adjusted incidence in both studies [3].

Possible differences between KPSC and KPNC in determining BP exposure are worthy of comment. The KPSC analyses included few without BP exposure who experienced an AFF. When restricting observations to KPSC patients who received BP, prescriptions were evaluated retrospectively to 1996, > 10 years preceding 2007–2011 (when cohort and AFF events were identified). The KPSC AFF cases were also counted if they occurred after last BP use, including 6 AFF cases (5% of 128 AFF) occurring ≥ 1 year after BP cessation. In contrast, KPNC identified women retrospectively but followed them forward from BP initiation (2002–2014). Thus, data on BP exposure and AFF events were captured in parallel, possibly contributing to the higher crude incidence of AFF. While AFF cases occurring < 1 year after BP cessation were included in KPNC's analyses, the 6 cases (5%) occurring ≥ 1 year following BP cessation were not. The KPNC study also examined the magnitude of cumulative treatment gaps and found that for patients who continued treatment beyond 2 years, the days' supply accounted for two-thirds of the overall exposure period (first to last BP prescription). These findings suggest that extremely large treatment gaps are likely not occurring in the vast majority with ongoing BP treatment.

When comparing crude and age-adjusted incidences of AFF, Dell and colleagues found a 2 to 3-fold higher age-adjusted incidence of AFF among those who received ≥ 8 years of BP therapy, whereas we found a 40–50% lower age-adjusted incidence of AFF compared to the crude rate.

These observations may be due to age differences; KPSC women experiencing AFF were on average 5 years younger at the time of fracture (mean age 69.3 ± 8.6) [3] than KPNC women. The KPSC study spanned an earlier era where women were younger when initiating BP initiation. Overall, taking age into consideration and comparing longer (> 8 years) versus shorter (< 4 years) exposure, we see an 8 to 10-fold greater age-adjusted incidence of AFF in KPSC and KPNC. The similarities are notable. Both studies indicate that after 4–6 years of BP exposure, there is a substantial and worrisome increase in this late complication.

A limitation of our study is that partial AFF cases were not examined due to the lack of specific ICD-9 coding for diaphyseal stress fractures until recent years and lack of systematic screening for partial AFF. Only four cases of partial/incomplete AFF among those without complete AFF were identified but not included in our analyses. A few AFFs may have been missed due to coding error or lack of imaging. It is possible that BP prescriptions were obtained outside our health plan, although patients are financially incentivized to use KPNC pharmacies and mailed prescription services. We also did not study AFF risk associated with intravenous BP or denosumab, nor the risk after transitioning to these therapies. Finally, our study, conducted in northern California, may not be generalizable to other US regions where the percentage of Asians is lower. Both northern and southern California regions have relatively high percentages of women of Asian race, a known demographic risk factor for AFF [5, 11].

In summary, our understanding of BP exposure and AFF risk has evolved considerably since these unusual fractures were first reported in 2005 [1]. Now in 2019, an association is widely accepted, although the potential causal mechanism(s) are not fully understood. It has been proposed that chronic suppression of bone turnover changes the bone quality and impairs micro-crack repair in susceptible patients, which in concert may allow pathologic extension of unimpeded crack progression in areas of high mechanical stress [13]. Whatever the ultimate mechanisms responsible, providers need to be aware of the importance of treatment duration. Warnings from the Food and Drug Aministration [14] and recommendations from some experts [15] advocate limiting BP exposure to 5 years, except where high fracture risk justifies extended use for possible long-term benefit. For patients who continue treatment beyond 5 years, the current study and that of Dell and colleagues [3] provide compelling evidence for progressive time-related accrual of risk that may be as high as 1 in 1000 after 8 years, an absolute risk that is not rare and should be further examined in high-risk demographic subgroups to better inform long-term treatment decisions.

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Compliance with ethical standards

The study was approved by the KPNC Institutional Review Board, and the requirement for informed consent was waived due to the nature of the study.

Conflict of interest Joan Lo has received past research funding from Amgen and Sanofi and Malini Chandra has received past research funding from Amgen, not pertaining to this study. Bruce Ettinger has served as an expert witness pertaining to litigation involving teriparatide (Teva Pharmaceuticals). Dr. Ott previously attended a scientific advisory meeting for Amgen but declined the honorarium. The remaining authors have no conflict of interest to disclose.

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