




Bisphosphonate treatment and the risk of atypical femoral fracture among patients participating in a Fracture Liaison Service of a tertiary medical center

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Abstract

Summary Bisphosphonates are common treatment for osteoporosis. Among patients admitted with hip fracture, atypical femoral fractures (AFF) were more prevalent in those who were treated with Bisphosphonates for five or more years. Five years of Bisphosphonates treatment may signify an increased risk for AFF, though the absolute risk remains very low.

Purpose Atypical femoral fractures (AFF) are a rare complication of bisphosphonate (BP) treatment. We evaluated the correlation between BP exposure and AFF risk among hip fracture patients.

Methods This retrospective nested case–control study included patients over age 50 years, operated for osteoporotic hip fracture between July 2014 and November 2018, who attended our Fracture Liaison Service. We classified fracture radiographs and compared demographic, clinical, biochemical, and drug purchase data between patients with AFF and those with typical osteoporotic hip fracture (controls). To correct for the younger age of patients with AFF, we matched each case (AFF) with three controls according to age (± 1 year) and sex and performed a conditional logistic regression model.

Results Of 989 patients, 31 (3%) had AFF. Patients with AFF were younger than those with inter-trochanteric fractures (mean \pm SD: 72.3 \pm 10.3 vs. 80.2 \pm 9.6 years, $p < 0.001$). Following matching, the mean Charlson's Comorbidity Index (CCI) was lower in the AFF than in the control group (2.9 \pm 3.7 vs. 4.7 \pm 4.2; $p = 0.030$) and a higher proportion of them were treated with BP for 5 years or more (58.1 vs. 16.0%; $p < 0.001$). Among patients admitted with hip fracture who were treated with BP for 5 years or more, the odds ratio of this fracture being atypical was significantly higher compared with no BP treatment (21.7; 95% CI-4.1–113.9).

Conclusions Patients with AFF compared to typical hip fractures showed better baseline medical conditions irrespective of their younger age. Five years of BP treatment may be associated with an increased risk for AFF, though the absolute risk remains very low.

Keywords Atypical femoral fracture · Bisphosphonate · Osteoporosis · Fracture Liaison Service

Merav Fraenkel and Uri Yoel are equal contribution as the last author.

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Introduction

Osteoporosis is a systemic skeletal disorder, manifested by increased fracture risk [1]. About one of every two Caucasian women and one of five Caucasian men experience an osteoporosis-related fracture during their lifetimes [2]. Bisphosphonates (BP), bone antiresorptive drugs, are the pillar stones of the medical treatment of osteoporosis. These drugs reduce osteoclasts number and activity and thus decrease bone turnover. This results in increased bone mineral density and reduction in fracture risk by 30–70% [3–7].

In the past decade, BP treatment has been shown to be associated with atypical femoral fractures (AFFs), which

are rare fractures with a transverse morphology [8]. AFF pathogenesis is considered as the development of an unhealed stress fracture [9]. In the physiological state, a stress fracture is usually followed by normal bone remodeling and healing. Long-term use of BP impairs the capacity of this natural repair process and rarely results in atypical fragility fractures [8, 10–13]. The estimated incidence of AFF is 1.8/100,000 patient years after 2 years of BP treatment, 16/100,000 patient years after 5 years of treatment, and 113/100,000 after 10 years of treatment [14–16]. It should be emphasized however that the absolute risk of AFF remained very low as compared with reductions in the risk of hip and other fractures with BP treatment [17]. Due to this established correlation between the duration of BP treatment and AFF, current guidelines suggest a “drug holiday,” after 3–5 years of BP treatment [7, 15]. It was shown that even few months of “drug holiday” may reduce significantly the risk of AFF among patients who were treated with BP [17]. Additional risk factors for AFF may include diabetes mellitus, rheumatoid arthritis, and medical treatment with glucocorticoid and proton pump inhibitors (PPI) [18–20]. Asian ancestry, higher BMI, and specific femoral geometry (e.g., proximal femoral varus) have also been associated with increased risk of AFF [15, 17, 18, 21].

In this retrospective study, we aimed to characterize AFF among patients who attended a tertiary care hospital fracture liaison service (FLS). We compared the rates and durations of BP exposure, as well as demographic, clinical, biochemical, and radiological characteristics, and drug purchase data between patients with AFF (cases) and patients with typical osteoporotic hip fractures (controls). We examined two hypotheses. Our first hypothesis was that patients with AFF would have distinct demographic and clinical characteristics compared with patients with typical osteoporotic hip fractures, regardless of the specific site of these typical fractures. Second, we hypothesized that the risk of AFF among patients admitted to our institution with osteoporotic hip fracture would be greater among those treated with BP and would increase from a certain point of time during the course of BP exposure.

Methods

Study population

This is a retrospective, nested case–control study of patients treated at Soroka University Medical Center, a 1100-bed teaching, tertiary care referral hospital in Beer-Sheva, Israel. Patients over age 50 years, admitted to our institution with low trauma hip fracture from July 2014 to November 2018,

were offered evaluation, follow-up, and treatment by our FLS. Patients were not offered to attend the service if they had a severe comorbidity (e.g., active malignancy, end-stage kidney disease treated by hemodialysis), had not undergone an operation for the fracture, had difficulty communication, or were not living in the district. In addition, patients did not attend our FLS if they were insured by a health maintenance organization other than Clalit Health Services. This is because we did not have pre-admission data for those patients, and follow-up and treatment in our institution were not covered by their health maintenance organizations. We excluded from the current analysis patients with device-associated fractures and patients with incomplete data.

Data captured

Demographic, clinical, biochemical, radiological, and drug purchase data of all the individuals in the cohort were collected from a unified electronic medical file and reviewed. The unified medical files included all the hospital and community records of each patient. Past medical diagnoses were used to calculate Charlson’s Comorbidity Index (CCI) [22]. Laboratory results of hemoglobin and creatinine were retrieved from the computerized data of admissions with hip fracture. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD equation [23]. Parathyroid hormone (PTH) and 25(OH)-vitamin D serum levels were retrieved from 6 months prior and up to 1 month after the index admission. Drug purchase data were retrieved and analyzed up to 5 years prior to the index admission with an osteoporotic hip fracture. One year of BP treatment was defined as a period of at least 6 months of purchase of oral preparations or one purchase of zoledronic acid per year, as was defined by others [24–26]. For medications other than BP, we classified any purchase during 5 years before the fracture as a positive result and no purchase as a negative result.

Radiographic assessment

From review of lower extremity radiographs and surgical records of patients admitted with low trauma hip fracture, we classified AFF based on the revised definition of the American Society for Bone and Mineral Research [9]. Accordingly, the fracture is located along the femoral diaphysis, from just distal to the lesser trochanter to just proximal to the supracondylar flare. In addition, at least three of four major radiographic features must be present: (1) the fracture line originates at the lateral cortex and is substantially transverse in its orientation; (2) complete fractures extend through both cortices and may be associated with a medial spike, while incomplete fractures involve only the lateral cortex; (3) the

fracture is non-comminuted or minimally comminuted; and (4) localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site.

All fractures that were not classified as AFF were considered typical osteoporotic hip fractures, based on the guidelines of the American Association of Clinical Endocrinologists [27]. To address our first hypothesis that patients admitted with AFF had distinct demographic, clinical, and biochemical characteristics compared with patients admitted with typical osteoporotic hip fractures, regardless of the specific site of these typical fractures, we subdivided the latter according to the site of fracture: (1) femur neck (sub-capital and trans-cervical, not involving the trochanteric area); (2) inter-trochanteric; and (3) sub-trochanteric, not classified as AFF, and not involving the greater or lesser trochanter. Bilateral and recurrent fractures were documented separately.

Hip fracture images of all the patients were reviewed by our research team, which included a radiologist and an endocrinologist. The reviewers were blinded to BP treatment status. Images were viewed on our hospital picture archival and communication system (PACS). Radiographic images were magnified in order to detect and accurately classify the fractures. Following review by the study team, fracture classifications were compared with the ICD-9 code of the discharge diagnosis from the orthopedic department. In cases of discordance between the ICD-9 discharge code and our diagnosis, we used a consensus decision method among our research team members.

Statistical analyses

Baseline demographic, clinical, and medical characteristics and blood test results were summarized using descriptive statistics. Patients with AFF were compared with the 3 subgroups of patients with typical osteoporotic hip fractures using the ANOVA test or the Kruskal–Wallis test, as appropriate. Categorical data were compared using the χ^2 test or Fisher's exact test. A p value < 0.05 was considered statistically significant. We aimed to detect differences in BP exposure between patients with a fracture classified as an AFF and patients with typical osteoporotic hip fractures (the control group). The probability for AFF in patients admitted with hip fractures according to their BP exposure time was assessed in two models. The first model compared the AFF group ($n = 31$) with the entire typical osteoporotic hip fracture group ($n = 958$). To correct for the younger age of patients with AFF, a second model was used. We randomly matched each case (AFF) with three controls according to age (± 1 year) and sex. We used conditional logistic regression models for the multivariable analysis. Each time period of BP treatment prior to fracture has been analyzed separately. We examined four time-periods: any BP exposure, 2 years or less out of the 5 years prior to fracture, between

2 and 5 years prior to fracture and lastly, and 5 years or longer prior to fracture. We presented the models once with a BP exposure window without adjustment and second, following adjustment to the variables that were found to differ significantly between cases (AFF) and controls. Statistical analysis of pooled data was performed using SPSS version 25.0 (SPSS, Chicago, IL).

Ethics statement

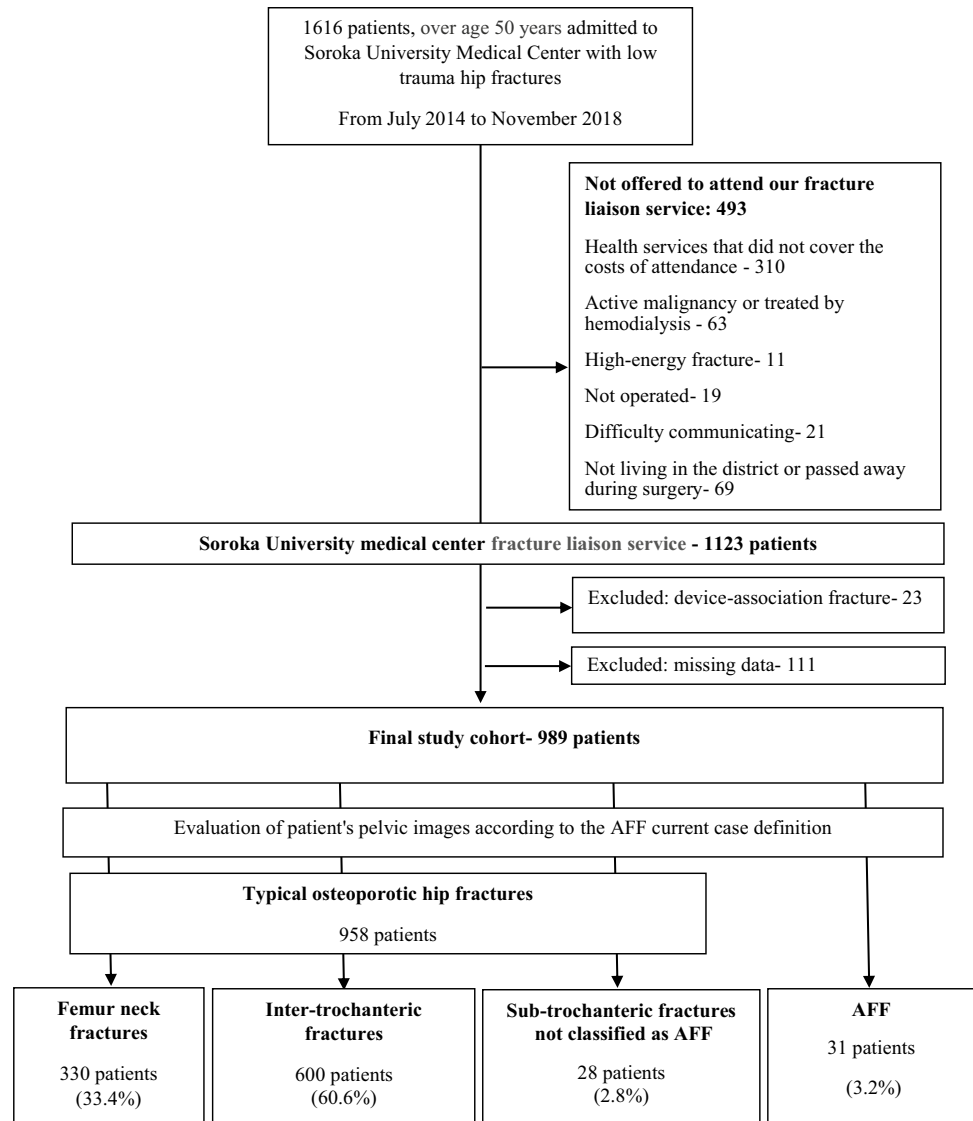
The study was approved by the Helsinki committee of Soroka University Medical Center (SCRC-170–19). The requirement for informed consent was waived due to the retrospective nature of the study.

Results

Baseline characteristics

During the study period, 1616 patients over age 50 years were admitted to our institution with low trauma hip fracture. Of these, 1123 patients were offered to attend our FLS. Following exclusion of 23 patients with device-associated fractures and 111 patients with missing data (mainly due to low-quality radiographs), the final study cohort consisted of the 989 patients whose full data were available to us (Fig. 1). Radiographic assessment classified 31 (3%) as having an AFF, of whom 1 was incomplete fracture, 330 (33%) with femur neck fractures, 600 (61%) with inter-trochanteric fractures, and 28 (3%) with sub-trochanteric fractures not classified as AFF and not involving the greater or lesser trochanter. Baseline characteristics according to the site of fracture are presented in Table 1. Overall, 71% of the patients were women. Patients who presented with AFF (mean age \pm SD: 72.3 ± 10.3 years) were younger than those who presented with femur neck fractures (78.0 ± 10.3) and younger than those with inter-trochanteric fractures (80.2 ± 9.6); $p = 0.004$ and $p < 0.001$ for the respective comparisons. Patients with AFF showed a better medical condition at baseline as was demonstrated by a statistically significant lower mean CCI (2.9 ± 3.7) than patients with femur neck fractures (4.9 ± 5.1), inter-trochanteric fractures (5.5 ± 4.3), and non-AFF sub-trochanteric fractures (5.2 ± 4.3), $p = 0.028$, $p = 0.001$, and $p = 0.029$ for the respective comparisons. Rates of any duration of PPI treatment within the 5 years prior to fracture were lower in patients with AFF (18.8%) than in patients with femur neck fractures (46.7%) and lower than in patients with inter-trochanteric fractures (50.9%), $p = 0.004$ and $p < 0.001$ for the respective comparisons. Other suggested risk factors for AFF, such as diabetes mellitus and treatment with glucocorticoids, were not found to

Fig. 1 Study flow chart



be statistically different between the AFF group and each of the subgroups of typical osteoporotic hip fractures. The mean hemoglobin level at admission was higher among patients with AFF (13.4 ± 1.2 gr/dL) than among those with inter-trochanteric fractures (12.04 ± 1.9 gr/dL) and higher than among those with non-AFF sub-trochanteric fractures (11.9 ± 1.2), $p = 0.018$ and $p = 0.024$ for the respective comparisons. Other lab test results, including creatinine, eGFR, PTH, and 25(OH)-vitamin D levels, did not differ between the groups.

According to the matched groups (Table 2), the mean CCI of patients with AFF was significantly lower than that of patients with typical osteoporotic hip fractures (2.9 ± 3.7 vs. 4.7 ± 4.2 ; $p = 0.030$). In addition, rates of PPI treatment were lower in the AFF group (18.8% vs. 51.6% $p = 0.002$). Differences between the groups were not significant in the other parameters examined, including

hemoglobin level, eGFR, PTH and 25(OH)-vitamin D levels, diabetes mellitus status, and glucocorticoid treatment.

BP exposure

Computerized data of BP purchases were available for 5 years prior to the fracture date for patients with all fracture types. We compared the duration of BP exposure between patients diagnosed with AFF ($n = 31$) and those with typical osteoporotic hip fractures ($n = 958$) (Table 3). The proportion of patients treated with BP for 5 years or more was higher among those with AFF than among those with typical osteoporotic hip fractures (58.1 vs. 16.0%; $p < 0.001$). The only incomplete AFF patient was under prolonged BP treatment of 5 years or more.

Odds ratios (ORs) for the risk for AFF at admission with hip fracture for the entire cohort and for the matched

Table 1 Baseline characteristics of patients included in the final study cohort according to the site and type of fracture

	Typical osteoporotic hip fracture			AFF n = 31	p value
	Femur neck fractures n = 330	Inter-trochanteric fractures n = 600	Sub-trochanteric, not classified as AFF n = 28		
Age (years) mean ± SD	78.0 ± 10.3	80.2 ± 9.6	76.7 ± 11.8	72.3 ± 10.3	^a 0.004 ^b < 0.001 ^c 0.145
Sex, female n, %	226 (68.5)	428 (71.3)	23 (88.5)	26 (83.9)	^a 0.074 ^b 0.130 ^c 0.619
Creatinine (mg/dL)	0.9 ± 0.6	0.98 ± 0.4	0.8 ± 0.4	0.8 ± 0.2	^a 0.404 ^b 0.122 ^c 0.574
eGFR (mL/min), mean ± SD	82.09 ± 29.4	78.6 ± 33.9	80.4 ± 20.6	87.6 ± 31.3	^a 0.552 ^b 0.393 ^c 0.599
Hb (g/dL) mean ± SD	12.6 ± 1.7	12.04 ± 1.9	11.9 ± 1.2	13.4 ± 1.2	^a 0.118 ^b 0.018 ^c 0.024
PTH (pg/dL) mean ± SD	102.5 ± 137.6	107.8 ± 93.4	87.9 ± 54.4	97.4 ± 50.4	^a 0.918 ^b 0.756 ^c 0.740
Vitamin D (nmol/L) mean ± SD	45.5 ± 25.3	42.4 ± 21.6	45.8 ± 30.3	45.1 ± 15.2	^a 0.963 ^b 0.730 ^c 0.958
Diabetes mellitus n (%)	79 (23.9)	210 (35.0)	9 (32.1)	7 (22.6)	^a 0.865 ^b 0.156 ^c 0.409
Charlson's comorbidity index mean ± SD	4.9 ± 5.1	5.5 ± 4.3	5.2 ± 4.3	2.9 ± 3.7	^a 0.028 ^b 0.001 ^c 0.029
Any treatment with BP ^d n (%)	37 (11.2)	169 (28.2)	7 (25.0)	20 (64.5)	^a < 0.001 ^b < 0.001 ^c 0.001
PPIs n (%)	172 (46.7)	324 (50.9)	9 (32.1)	6 (18.8)	^a 0.004 ^b < 0.001 ^c 0.158
Steroids n (%)	81 (22.0)	164 (25.8)	10 (35.7)	10 (32.2)	^a 0.170 ^b 0.494 ^c 0.573
Anti-depressants n (%)	60 (16.3)	102 (16.0)	6 (21.4)	3 (9.7)	^a 0.368 ^b 0.335 ^c 0.117
Statins n (%)	202 (54.9)	370 (58.2)	16 (57.1)	15 (48.4)	^a 0.532 ^b 0.258 ^c 0.501

AFF atypical femoral fracture, PTH parathyroid hormone, Vit D- 25(OH)-Vitamin D, BP bisphosphonate, PPI proton pump inhibitors

p value for the comparison between patients admitted with AFF and those who were admitted with typical osteoporotic hip fracture according to its site: ^a for femur neck fractures, ^b inter-trochanteric fractures, and ^c for sub-trochanteric fracture not classified as AFF

^dOne or more purchases of BP

group, according to the length of BP exposure time, are presented in Table 4. In both models, the adjusted OR of being admitted with AFF increased as the number of BP treatment years increased, becoming statistically significant for 5 years of treatment or more (adjusted OR using the model

that included the entire cohort- 19.34; 95% CI-7.84–47.93 and 21.7; 95% CI-4.1–113.9 for the matched cohort model). For patients treated with BP for more than 2 years and less than 5 years, the trend for increased risk did not reach statistical significance. The risk of being admitted with AFF

Table 2 Baseline characteristics of patients included in the final study cohort following 3:1 matching of typical osteoporotic hip fracture to atypical femoral fractures for age (± 1 year) and sex

	Typical osteoporotic hip fracture <i>n</i> = 93	AFF <i>n</i> = 31	<i>p</i> value
Age (years) mean \pm SD	72.4 \pm 9.4	72.3 \pm 10.3	0.991
Sex, female <i>n</i> , %	78 (83.9)	26 (83.9)	1.000
Creatinine (mg/dL)	1.04 \pm 1.05	0.8 \pm 0.2	0.409
eGFR (mL/min) mean \pm SD	90.5 \pm 44.3	87.6 \pm 31.3	0.848
Hb (g/dL) mean \pm SD	12.3 \pm 2.1	13.4 \pm 1.2	0.118
PTH (pg/dL) mean \pm SD	120.8 \pm 112.69	97.4 \pm 50.4	0.579
Vit D (nmol/L) mean \pm SD	45.2 \pm 21.09	45.1 \pm 15.2	0.994
Diabetes mellitus <i>n</i> (%)	33 (35.5)	7 (22.6)	0.183
Charlson's Comorbidity Index mean \pm SD	4.7 \pm 4.2	2.9 \pm 3.7	0.030
Any treatment with BP ^a <i>n</i> (%)	20 (21.5)	20 (64.5)	<0.001
PPIs <i>n</i> (%)	48 (51.6)	6 (18.8)	0.002
Steroids <i>n</i> (%)	27 (29.0)	10 (32.2)	0.734
Anti-depressants <i>n</i> (%)	20 (21.5)	3 (9.7)	0.142
Statins <i>n</i> (%)	61 (65.6)	15 (48.4)	0.089

AFF atypical femoral fracture, PTH parathyroid hormone, Vit D-25(OH)-Vitamin D, BP- bisphosphonate, PPI proton pump inhibitors

^aOne or more purchases of BP prior to hip fracture

Table 3 Bisphosphonate treatment years among patients included in the final study cohort, according to the type of fracture^a

Years of treatment with BPs ^b	Typical osteoporotic hip fracture <i>n</i> = 958	AFF <i>n</i> = 31	<i>p</i> value
1 year <i>n</i> (%)	10 (1.0)	0 (0.0)	0.567
2 years <i>n</i> (%)	21 (2.2)	1 (3.2)	0.701
3 years <i>n</i> (%)	14 (1.5)	0 (0.0)	0.498
4 years <i>n</i> (%)	15 (1.6)	1 (3.2)	0.471
5 years or more <i>n</i> (%)	153 (16.0)	18 (58.1)	<0.001
Any treatment with BP ^c <i>n</i> (%)	213 (22.2)	20 (64.5)	<0.001

AFF atypical femoral fracture, BP bisphosphonate

^aComputerized BP purchase data were available for 5 years prior to the fracture date

^bA year of BP treatment was defined as a period of 6 months and more of oral BP purchase per year or one purchase of zoledronic acid per year

^cOne or more purchases of BP

was higher in the adjusted models than in the unadjusted models (Table 4).

Discussion

This case control study showed that patients with AFF (cases) were younger and in better medical condition at baseline than patients with all other sites of typical osteoporotic hip fracture (controls). This was evident from a statistically significant lower value of CCI. CCI remained significantly lower ($p=0.03$) following 1:3 matching for age (± 1 year) and sex, of cases with controls. These results, taken together, concur with our first hypothesis that patients admitted with AFF had distinct demographic and clinical characteristics compared with patients admitted with typical osteoporotic hip fractures. We also found that a higher proportion of cases than controls had been treated with BP for 5 years or more (58.1 vs. 16.0%; $p < 0.001$). A multivariate analysis of patients matched for age and sex found that the OR for being admitted with an AFF, adjusted for CCI and any duration of PPI treatment, increased as the number of BP treatment years increased and reached statistical significance after 5 years or more of treatment (OR-21.7; 95% CI-4.1–113.9). A second multivariate analysis for the entire cohort, adjusted for sex, age, CCI, and any duration of PPI treatment showed comparable results (adjusted OR-19.34; 95% CI-7.84–47.93) and, thus, reassure the concern regarding selection bias of using the matched group model. These findings address our second hypothesis, as to the risk of AFF in relation to the length of BP exposure. Our results demonstrated that 5 years of BP treatment may represent a point of time at which the risk of AFF should become a significant consideration in decisions about treatment management. Moreover, though not statistically significant, our results suggest that the critical point for decision making may occur even earlier, between 2 and 5 years of treatment. These results are congruent with previous studies that suggested an exponential correlation between the duration of BP exposure and the risk of AFF [14, 15, 17].

Our study is consistent with a number of reports that showed a younger age of patients with AFF than with typical osteoporotic hip fractures [9, 11, 18]. Associations of other risk factors with AFF are controversial. We found a lower rate of any duration of PPI treatment among patients admitted with AFF. This contrasts with others who demonstrated higher rates of PPI treatment among patients admitted with AFF, compared with typical osteoporotic hip fracture [11, 18]. However, since according to our methods any duration of PPI treatment within the 5 years prior to hip fracture was considered as "positive" for PPI treatment, it is questionable whether this observation has clinical significance.

Table 4 Odds ratios (95% CI) for the risk of atypical femoral fracture at admission with hip fracture among the entire cohort^a and the matched cohort^b, according to the exposure time to bisphosphonates

	All cohort patients ^a		Matched ^b for age and sex	
	Unadjusted	Adjusted ^c	Unadjusted	Adjusted ^d
Any BP exposure	6.36 (3.00–13.48)	9.25 (3.39–21.77)	5.6 (2.1–14.7)	11.6 (3.0–44.4)
BP treatment for 2 years or less	1.52 (0.45–5.14)	1.69 (0.47–5.99)	1.3 (0.3–5.3)	1.3 (0.3–5.9)
BP treatment for more than 2 years and less than 5 years	2.12 (0.62–7.24)	2.64 (0.73–9.58)	1.9 (0.4–8.8)	6.6 (0.9–45.5)
BP treatment for 5 years or more	12.09 (5.63–25.97)	19.34 (7.84–47.93)	10.6 (2.9–37.6)	21.7 (4.1–113.9)

^aThirty-one patients with atypical femoral fracture were compared to 958 patients with typical osteoporotic hip fracture

^bWe randomly matched one case of atypical femoral fracture with three controls with typical osteoporotic hip fracture based on age (± 1 year) and sex

^cAdjusted for age, sex, proton pump inhibitor treatment, and Charlson's Comorbidity Index

^dAdjusted for proton pump inhibitor treatment and Charlson's Comorbidity Index

Treatment with glucocorticoids (GC) is another controversial, yet commonly reported risk factor for AFF [9, 11, 17, 18, 21]. We did not find an association of any GC treatment with increased risk of AFF compared with typical osteoporotic hip fractures. Our findings concur with those of a retrospective Korean study [11] but contrast with those of a retrospective Canadian study that showed a higher rate of GC treatment among patients admitted with AFF than with other fractures [18]. A recent, large, well-designed retrospective study, by Black et al., has convincingly shown that the risk of AFF, among women treated with BP, increased significantly after one or more years of GC treatment [17]. A possible explanation for the discrepancy between the studies is the lack of information regarding the duration of GC treatment in our study and others [11, 18]. Accordingly, studies aimed to evaluate the added risk of GC to the development of AFF should include data regarding treatment duration with both drugs [28].

This study has several limitations. First, data collection was retrospective. A prospective evaluation may have achieved better quality data. Second, our cohort does not represent either the general population or the population of patients with osteoporosis. More specifically, our cohort represents high-risk osteoporotic patients [7] who were admitted to our institution with hip fracture. Accordingly, we do not claim that the increased risk found in our study represents the risk of having an AFF following certain BP exposure time in the general osteoporotic population but rather the risk of AFF among patients over age 50 years, admitted with low trauma hip fracture. Third, pre-treatment bone mineral density (BMD) measurements were available for only few patients in our cohort (less than 20%). Therefore, we could not completely exclude the possibility of reverse causality, in which the patients on longer treatment with BP are those with more severe osteoporosis. However, the lower CCI in patients with AFF shown in our study suggests that the overall morbidity load was lower in the AFF group compared

with typical osteoporotic hip fractures. We assumed that this better medical condition is also applicable to the AFF patient's bone health status. The consistency of the CCI trend after adjustment to age and sex strengthens this assumption. Fourth, the number of patients with AFF in our study was small, due to the rarity of this condition. This resulted in numerically unequal "cases" and "controls" groups. We overcame this disparity by creating a control group that was randomly matched 3:1 for sex and age (± 1 year). Fifth, we could not determine the exact adherence of each individual patient to BP treatment, as well as to treatment with other medications of interest, such as PPIs and glucocorticoids. Finally, a possible selection bias arises in that 310 patients were excluded from the analysis due to their being insured by a health medical organization for which we did not have drug purchase data. There is no reason to believe that their characteristics differed from the patients included in the cohort.

Despite the above limitations, this study has important strengths. The unified electronic medical files, used in our hospital and in the community medical services, enabled access to all recorded information of all the patients in our fracture liaison service. Specifically, we could easily calculate the CCI [22], a well validated index for comorbidities. Additionally, the femoral fracture images of all our patients were reviewed by the same research team members, including a radiologist and an endocrinologist, blinded to BP treatment status. The classification of the typical femoral hip fractures into subgroups and the assessment of each group separately strengthen the credibility of our hypothesis, namely that patients admitted with AFF had distinct characteristics, compared with patients admitted with typical osteoporotic hip fractures, regardless of the specific site of these typical fractures.

In conclusion, our study showed that patients with AFF compared to typical hip fractures showed better baseline medical conditions irrespective of their younger age. A higher proportion

of patients with AFF than patients with typical osteoporotic hip fractures was treated by BPs for 5 or more years prior to their fractures. Further, the risk of AFF, though absolutely low, increased as the number of BP treatment years increased and reached statistical significance after 5 years of treatment. This finding concurs with the rationale of current guidelines, which suggests a “drug holiday” after 3–5 years of BP treatment, for patients with a mild to moderate fracture risk [7, 15, 29]. Nevertheless, the beneficial effect of BP treatment on the risk of vertebral and non-vertebral typical osteoporotic fractures should be considered when decisions on “drug holiday,” and its duration is taken [17]. To overcome the limitations of our study, a large, prospective study that follows patients treated with BP, including adherence data, is needed. This will enable drawing more precise conclusions regarding the time point during BP treatment at which the risk of AFF becomes significantly elevated.

Author contribution Noa Bareli—study design, radiograph images assessment, analysis and interpretation of data, manuscript writing.

Roni Gat—study design, acquisition of data, analysis and interpretation of data, approval of the manuscript final version.

Victoria Makarov—radiograph images assessment, analysis and interpretation of data, approval of the manuscript final version.

Ethel Siris—analysis and interpretation of data, revision of the manuscript, approval of the manuscript final version.

Merav Fraenkel—study design, analysis and interpretation of data, manuscript writing and approval.

Uri Yoel—study design, radiograph image assessment, analysis and interpretation of data, manuscript writing and approval.

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Availability of data and material Data is available upon the request and according to the national policy of data sharing requiring authorization by ethics committee.

Code availability Not applicable.

Declarations

Conflict of interest Noa Bareli, Roni Gat, Victoria Makarov, Ethel Siris, Merav Fraenkel, and Uri Yoel declare that they have no conflict of interest.

Ethical approval The study was approved by the Helsinki committee of Soroka University Medical Center (*SCRC-170-19*). The requirement for informed consent was waived due to the retrospective nature of the study.

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