Risk of subtrochanteric and femoral shaft fractures due to bisphosphonate therapy in asthma: A population-based nested case-control study.

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CONFLICT OF INTEREST

Christos V. Chalitsios, Dominick E. Shaw, and Tricia M. McKeever declare that they have no conflict of interest.

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ABSTRACT

Introduction

Bisphosphonates are used as first-line treatment for osteoporosis; however, concerns have been raised over their association with atypical subtrochanteric (ST) and femoral shaft (FS) fractures. The potential risk of atypical ST/FS fractures from bisphosphonate use in asthma has not been examined.

Methods

A nested case-control study was conducted using linked data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) databases. Using an asthma cohort, we identified patients with atypical ST/FS fractures and sex, age, and practice-matched controls. Conditional logistic regression was used to determine the association between bisphosphonate exposure and atypical ST/FS fractures.

Results

From a cohort of 69074 people with asthma, 67 patients with atypical ST/FS fractures and 260 matched control subjects were identified. Of the case patients, 40.3% had received bisphosphonates as compared with 14.2% of the controls corresponding to an adjusted odds ratio (aOR) of 4.42 (95%CI, 2.98 to 8.53). The duration of use influenced the risk with long-term users to be at a greater risk (> 5 yrs. vs no exposure; aOR= 7.67; 95%CI, 1.75 to 33.91). Drug withdrawal was associated with diminished odds of atypical ST/FS fractures.

Conclusion

Regular review of bisphosphonates should occur in patients with asthma. The risks and benefits of bisphosphonate therapy should be carefully considered in consultation with the patient. To improve AFF prevention, early signs which may warrant imaging, such as prodromal thigh pain, should be discussed.

MINI-ABSTRACT

Concerns have been raised over the association between bisphosphonates and atypical fractures in subtrochanteric and femoral shaft regions but the potential risk of these fractures due to bisphosphonate use in asthma has not been examined.

Keywords: Asthma, Bisphosphonates, risk, subtrochanteric fractures, femoral shaft fractures.

INTRODUCTION

Studies report people with asthma are at greater risk of osteoporosis and fragility fractures (1) associated with inhaled (ICS) and oral (OCS) corticosteroid use.(2) Bisphosphonates are recommended as the first-line drugs for bone protection. However, in 2006 concerns were raised when bisphosphonate use was associated with unusual fractures (transverse morphology, thickened cortex, occurring either spontaneously or with low trauma) in the subtrochanteric (ST) and femoral shaft (FS) regions (3); together these are now known as atypical femoral fractures (AFF) . We set out to examine the risk of atypical ST/FS fractures in asthma to guide the clinical use of bisphosphonates.

METHODS

A population-based nested case-control study was conducted utilising primary (Clinical Practice Research Datalink) linked to secondary care (Hospital Episode Statistics) databases. From a cohort of adult people with Read coded asthma between 1st April 2004 to 31st December 2017, cases were defined and indexed by the first Read or ICD-10 coded ST or FS fracture (Supplementary Table 1). Each case was matched with up to four randomly selected patients from the remaining patients with asthma based on age (±1 year), gender and practice. Conditional logistic regression was performed deriving unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) assessing the effect of bisphosphonate exposure (ever, total, dose, time, duration, and type) on the first ST or FS fracture after the Read coded asthma date (see also Supplementary Methods). The reference category for all analyses was no bisphosphonate exposure. All analyses were undertaken in R v4.0.3.

RESULTS

Characteristics of the study population

From a cohort of 69,074 people with asthma we identified 67 patients with asthma and atypical ST/FS fracture and 260 matched control subjects (Table 1). The vast majority were women (70.9% vs 29.1%) and the median age of the study population was 79.3 years (range, 68.4-86.7 years). Both a previous diagnosis of osteoporosis (aOR = 3.31; 95%CI 1.21 to 9.05) or fragility fracture (aOR = 4.17; 95%CI 2.46 to 9.00) were linked with an event of atypical ST/FS fracture.

Table 1. Characteristics of Patients with Subtrochanteric or femoral shaft fractures and Control Subjects.

Characteristic	Cases (N=67) n (%)	Controls (N=260) n (%)	Adjusted[b] OR (95%CI)
Age[a].			-
Mean ± SD	75.7 ± 14.2	75.7 ± 14.1	
Median (IQR)	79.3 (68.4-86.7)	79.3 (68.4-86.7)	
Sex			
Male	19 (28.4)	76 (29.2)	-
Female	48 (71.6)	184 (70.8)	-
Smoking status			
Never	19 (28.4)	126 (48.5)	1.00
Ex	39 (58.2)	94 (36.2)	4.53 (2.04 - 10.05)
Current	8 (11.9)	35 (13.5)	1.59 (0.53 - 4.77)
Missing status	1 (01.5)	5 (1.9)	2.58 (0.24 - 28.01)
BMI status, kg/m^2			
Underweight (<18.5)	3 (4.5)	7 (2.7)	7.05 (1.42 - 34.9)
Normal (18.5 – 24.9)	12 (17.9)	64 (24.6)	1.00
Overweight (25 – 29.9)	13 (19.4)	70 (26.9)	1.16 (0.44 - 3.11)
Obese (≥30)	23 (34.3)	70 (26.9)	1.79 (0.66 - 4.80)
Missing status	16 (23.9)	49 (18.9)	
Alcohol status			
Non-drinker	5 (7.5)	23 (8.9)	1.00
Ex-drinker	8 (11.9)	39 (15.0)	1.06 (0.26 - 4.39)
Current drinker	46 (68.7)	170 (65.4)	1.53 (0.50 - 4.70)
Missing status	8 (11.9)	28 (10.8)	1.47 (0.33 - 6.54)
IMD (Social Class)			
1 (least deprived)	12 (17.9)	47 (18.1)	1.00
2	16 (23.9)	72 (27.7)	0.52 (0.19 - 1.41)
3	13 (19.4)	41 (15.8)	1.50 (0.56 - 4.04)
4	12 (17.9)	48 (18.5)	0.91 (0.33 - 2.56)
5 (most deprived)	14 (20.9)	52 (20.0)	0.66 (0.24 - 1.84)
Charlson comorbidity index			.
1 (least comorbid)	27 (40.3)	123 (47.3)	1.00
2	10 (14.9)	38 (14.6)	1.16 (0.45 - 2.99)
3	10 (14.9)	36 (13.8)	1.32 (0.65 - 5.07)
4	8 (11.9)	28 (10.8)	1.81 (0.46 - 3.86)
≥5 (more comorbid)	12 (17.9)	35 (13.5)	2.18 (0.77 - 6.17)
Drug use in the year prior to the index date			
Oral corticosteroids	37 (55.2)	132 (50.8)	1.17 (0.61 - 2.26)
Vitamin D and/or calcium	29 (43.3)	66 (25.4)	1.06 (0.47 - 2.40)
Previous diagnoses			
Osteoporosis	16 (23.9)	17 (6.5)	3.31 (1.21 - 9.05)
Fragility fracture	31 (46.3)	36 (13.9)	4.17 (2.46 - 9.00)

Abbreviations: BMI, body mass index; IMD, Index of Multiple Deprivation.

[a] Age at the index date in years.

[b] Adjusted for smoking, body mass index, index of multiple deprivation, Charlson Comorbidity Index score, previous diagnosis of osteoporosis and fragility fracture, when not stratified by those.

Percentages have been rounded and might not total 100.

Bisphosphonates and risk of atypical ST/FS fractures

40.3% of the case patients had received bisphosphonates as compared with 14.2% of the controls (Table 2), corresponding to an adjusted odds ratio of 4.42 (95%CI, 2.98 to 8.53). The risk of atypical ST/FS fractures was higher with increasing number of bisphosphonate prescriptions, with an odds ratio of 10.01 (95% CI, 2.90 to 34.8) between 61 and 130 prescriptions. Similarly, the higher the bisphosphonate dose the greater the risk (16000mg vs no use: aOR=7.32;95% CI, 1.73 to 30.83). For duration of bisphosphonate use, the adjusted odds ratio as compared with no use ranged from 3.85 (95%CI, 1.47 to 9.99) for 1 year or less to 7.67(95%CI, 1.75 to 33.91) for 5 years or more. In the subgroup analyses both males and females had around the same odds of atypical ST/FS fracture, however people aged less than 80 years of age had an increased odds (aOR=11.12;95% CI, 3.35 to 36.91) compared to those aged 80 or more (aOR=2.78;95% CI, 1.16 to 6.67).

Table 2. Association between Bisphosphonate Exposure ever prior the index date and Risk of Subtrochanteric and Femoral Shaft Fracture.

	Cases		Controls		Age sex-adjusted	Adjusted[a]	
Type of exposure	**n**	**%**	**n**	**%**	**OR (95%CI)**	**OR (95%CI)**	**p-value**
Bisphosphonate use							
Never	40	59.7	223	85.8	1.00	1.00	
Ever	27	40.3	37	14.2	4.35 (2.23 – 8.26)	4.42 (2.98 - 8.53)	<.0001
Total prescriptions							.0015[b]
≤ 20	14	20.9	20	7.7	3.90 (1.80 - 8.45)	3.98 (1.80 - 8.77)	
21- 60	4	6.0	10	3.9	2.56 (0.74 - 8.84)	2.65 (0.73 - 9.59)	
61-130	9	13.4	7	2.7	10.13 (3.01 - 34.5)	10.01 (2.90 - 34.8)	
Cumulative alendronate dose, mg							.0244[b]
≤ 2200	6	9.8	7	2.8	4.14 (0.95 - 12.75)	4.63 (0.98 - 14.46)	
2201 – 8000	5	8.2	6	2.0	5.49 (1.41 - 21.33)	5.46 (1.36 - 21.86)	
8001 – 16000	5	6.6	9	3.2	2.55 (0.68 - 9.54)	3.48 (0.95 - 12.62)	
>16000	6	9.8	5	2.0	7.90 (1.90 - 33.13)	7.32 (1.73 - 30.83)	
Time since last use, yrs.							.001
≤ 0.5	20	29.8	21	8.1	5.80 (2.72 - 12.30)	5.76 (2.67 - 12.40)	
0.51 – 2	4	6.0	6	2.3	4.04 (1.08 - 15.10)	4.67 (1.19 - 18.40)	
>2	3	4.5	10	3.8	1.80 (0.45 - 7.06)	1.76 (0.44 - 7.00)	
Duration of use[c], yrs.							.0403[b]
≤1	9	13.8	13	5.1	3.81 (1.50 - 9.61)	2.85 (0.97 - 9.99)	
1.1-3	8	12.3	8	3.1	5.13 (1.77 - 14.83)	4.17 (1.78 - 15.24)	
3.1-5	3	4.6	7	2.8	2.08 (0.43 - 9.97)	2.28 (0.43 - 11.57)	
>5	5	7.7	4	1.6	8.03 (1.88 - 35.21)	7.67 (1.75 - 33.91)	
Type of bisphosphonate							
Alendronate	22	32.9	27	7.5	4.64(2.31- 9.31)	4.74 (2.31 - 9.72)	<.0001
Risedronate	5	7.5	1	0.4	4.08 (1.13 - 14.7)	3.98 (1.09 - 14.8)	.0370
Etidronate	0	0	2	0.8	NA	NA	
Ibandronate	0	0	7	2.6	NA	NA	

[a] *Adjusted for smoking, body mass index, index of multiple deprivation, Charlson Comorbidity Index score, previous diagnosis of osteoporosis - fragility fractures, and cumulative dose of OCS/ICS.*

[b] *P-value for trend.*

[c] *Was not able to determine duration for 7 individuals.*

Percentages have been rounded and might not total 100.

The reference category for all analyses was no bisphosphonate exposure.

DISCUSSION

This is the first study examining the association between bisphosphonates and atypical ST/FS fractures in asthma. We found that bisphosphonate exposure was associated with atypical ST/FS fractures. A clear dose-response relationship was found, with higher cumulative dose and long-term duration being associated with increased odds of atypical ST/FS fractures.

A meta-analysis in all patients using bisphosphonates found that the overall odds for any exposure and AFF was 11.12 (95%CI, 2.7 to 46.2) in the case-control studies, but 1.70 (95%CI 1.22 2.37) in the cohort studies (4). The authors suggested the overestimate in case-control studies may be due to the selection of the control group. Despite the differences in estimates, the main message was that the use of bisphosphonate was associated with larger atypical ST/FS fracture risk. Previous research also suggests increased risk of AFF with longer exposure (5).

Osteoporosis is a chronic condition that can require long term prophylactic treatment. We found that a bisphosphonate holiday was associated with decreased risk of atypical ST/FS fracture, consistent with other reports (6,7). However, the association was weaker in asthma because of the higher potential fracture risk (1). Two recent studies showed no or a minimal increase in the risk of hip or other fractures after bisphosphonate withdraw (8,9), suggesting that risk of atypical fractures should be balanced against the risk of hip and other fractures. It is currently recommended that patients using bisphosphonates between 3 and 5 years and are at low risk of common fractures can safely discontinue the treatment for around 2.5 years, but not for more than 5 years (10).

Even though the odds of atypical ST/FS fractures appeared increased in bisphosphonate users with asthma, the public health consequences are probably minor considering the rarity of these fractures compared to the usual fragility fractures, let alone in the first years of medication. In the examined cohort 2,131 fragility fractures were observed compared to 67 atypical ST/FS fractures (2). Consequently, our findings should not scare and discourage physicians and patients from using bisphosphonates when needed, as the risk of an osteoporotic fracture is much higher and immediate, especially in patients prescribed steroids (1). Specifically, among White women, the number of fractures prevented for each fracture type far outweighed bisphosphonate-associated atypical fractures at all time points. For example, after 3 years, there were 2 bisphosphonate associated atypical fractures as compared with 149 hip fractures prevented and 541 clinical fractures prevented. After 5 years, the respective numbers were 8, 286, and 859. The benefits remained in Asian and Hispanic women, but to a lesser extent than the Whites (5).

The population-based setting means the findings are generalizable to the wider population. Nevertheless, this study has some limitations. Diagnostic misclassification may occur. We could not ascertain the specific radiological features listed in the recent ASBMR Task Force Report on atypical femoral fractures (11). However, the ICD-10 codes for atypical ST/FS fractures have been validated showing a positive predictive value of 90% (95% CI, 88%-92%) and a sensitivity of 81% (95% CI, 78%-84%) (12). Similarly, Van Staa et al. carried out external validation of fracture diagnosis in CPRD and found that 91% of hip fracture (where atypical ST/FS fractures are located) diagnoses were verified by physicians (13). We also excluded Read coded fractures that may have occurred due to high-energy trauma. Nonetheless, the fact that we observed these fractures among bisphosphonate users is clinically important, independent of radiographic appearance. Finally, we recognise that those who are on bisphosphonates and longer exposure to bisphosphonates are likely to be those most at risk of fracture, however we tried to limit our fracture outcome to the 'atypical' fractures not usually found from osteoporosis risk.

Current national guidance on osteoporotic fracture risk reduction in asthma is limited even though this group of patients (with asthma) is different because of ongoing exposure to both inhaled and oral corticosteroids, hence one of the main risk factors for osteoporotic fracture cannot be avoided. BTS/SIGN says "*Bone mineral density should be monitored in adults. When a significant reduction occurs, treatment with a long-acting bisphosphonate should be offered*"; GINA states "*patients should be assessed and monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with a prescription of therapy for prevention of osteoporosis (where appropriate)*". Although the risk of osteoporotic fracture is mentioned, neither the duration of therapy and need for a drug holiday, nor the risk of AFF is discussed. Given that bisphosphonates are widely used in asthma we suggest that asthma guidance includes information on the management of AFF risk. This would include cessation of all bisphosphonates once an AFF is identified, avoidance of denosumab in any patient with AFF as it is a potent antiresorptive medication, but calcium and vitamin D should be continued. Patients with AFF should be investigated for secondary causes of osteoporosis and underlying metabolic bone disease. Bisphosphonates or denosumab should not be restarted after AFF, for at least 5 years. Appropriate exercise guidance is important for patients with AFF and imaging of the opposite femur to all patients with AFF may be warranted (11).

In conclusion, regular review of bisphosphonates should occur in patients with asthma. The risks and benefits of bisphosphonate therapy should be carefully considered in consultation

with the patient. To improve AFF prevention, early signs which may warrant imaging, such as prodromal thigh pain, should be discussed.

DECLARATIONS

FUNDING

The study was funded by the James Trust Research Grant a research award from British Medical Association (RB48DR).

ETHICS APPROVAL

The study was approved by the Independent Scientific Advisory Group of the CPRD (ISAC protocol number 19_041RA).

AUTHORS' CONTRIBUTION

CVC had full access to all the study data and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: CVC, DES, TMM; acquisition of data: CVC; analysis of data: CVC; interpretation of data: CVC, DES, TMM; drafting the article: CVC; revision for important intellectual content and approval of the version to be published: CVC, DES, TMM.

DATA AVAILABILITY

Data may be obtained from a third party and are not publicly available. This study is based on Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) data and is subject to a full license agreement which does not permit data sharing outside of the research team. However, data can be obtained by applying to CPRD (enquiries@cprd.com) for any replication of the study. The Read and ICD-10 codes used are available from the corresponding author upon reasonable request.

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Supplements

SUPPLEMENTARY METHODS

Source population

A population-based nested case-control study was conducted utilising the Clinical Practice Research Datalink GOLD, a large longitudinal primary care database,(1) linked to the Hospital Episode Statistics database.(2) The July 2018 dataset was used covering more than 15.4 million patients from 738 practices across the UK. The percentage of patients is approximately 7% of the UK population and they are representative with respect to age, gender and ethnicity of the wider UK people. Routinely collected clinical data generated from consultations, hospital discharges or specialist clinic letters are recorded using Read codes. HES is a secondary care database consisting of all hospitalisations in England, consequently only 60% of CPRD patients have linked data. HES contains diagnoses for each hospitalization episode, coded using the International Classification of Diseases version 10 (ICD-10).

Study population

All adult patients (≥18 years old) with a Read code for asthma between 1st April 2004 (activation of Quality and Outcomes Framework score) to 31th December 2017, with at least 1 year of data collection prior to the diagnosis of asthma date ensuring that only 'incident' cases were picked.(3) Only patients classed as "acceptable" research quality data and registered to an up-to standard practice were included according to CPRD's recommendations. Read codes for asthma have been previously validated against radiological reports.(4)

Cases, controls, and outcomes definition

In this nested case-control study cases were defined by the first-recorded Read or ICD-10 code of subtrochanteric or femoral shaft fracture (e-Table 1). The date of the first Read or ICD-10 coded subtrochanteric or femoral shaft fracture served as the index date for the cases. Each case was matched with up to four randomly selected patients from the remaining patients with

asthma by age (±1 year), gender and practice. The same index date was assigned to controls and cases. Read codes for fractures as well as the ICD-10 codes for ST/FS fractures have been previously validated against radiological reports.(5,6)

Potential confounders

For each participant in this study, we retrieved information on the following variables which are well-established risk for fracture or thought to have an impact on fracture risk and are also likely to be recorded within the databases: age at the index date; sex, including only those clearly classified as male or female; body mass index (BMI) using the nearest measurement prior the index date and categorised according to the World Health Organization (see Supplementary material); smoking and alcohol status using the nearest measurement ever prior to the index date (see Supplementary material); socioeconomic status measured by using the patient-level Index of Multiple Deprivation (IMD) 2015 in quintiles, with quintile 1 being the least and quintile 5 the most deprived. Patients with at least one prescription of oral corticosteroids, vitamin D and calcium the year prior the index date were also identified. Cumulative dose of ICS/OCS as a continuous variable was also considered. Finally, all patients with a previous diagnosis of osteoporosis or fragility fracture were extracted. The comorbidities were also summarised using the Charlson comorbidity index score.(7) If there was no record for a medication or diagnosis, patients were assumed to have not had the exposure.

Exposure assessment

Bisphosphonate exposure was identified via the prescription records. Bisphosphonates to be included were identified in the British National Formulary section 6.6.2 as treatment for osteoporosis: alendronate, etidronate, ibandronate, and risedronate. Bisphosphonate use was categorised in several ways. All prescriptions prior to the index date were identified. Initially, all patients with at least one prescription were extracted. Bisphosphonate use was also examined as the number of prescriptions filled. Bisphosphonates were grouped according to type as listed above. Where the type of bisphosphonate was changed during the year, we considered the most frequently prescribed. The bisphosphonates cumulative duration and dose in milligrams (mg) over the previous years was additionally assessed. To calculate the cumulative bisphosphonate dose, information from tablet strength (e.g. 70mg) and prescribed quantity was used, multiplying the quantity by strength for each prescription, and then all doses

per patient were summed. The time since last use of bisphosphonate prior to the fracture was calculated. There were not missing or implausible values in our specific patients' records of bisphosphonate use. The reference category for all analyses was no bisphosphonate exposure.

Statistical analysis

Descriptive statistics were used to summarise the characteristics of the cases and controls. To account for the matched design, we used conditional logistic regression deriving unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) assessing the effect of bisphosphonate exposure on the first subtrochanteric and femoral shaft fractures after the Read coded asthma date. Firstly, we performed a univariate analysis between the exposure and outcome of interest to establish the unadjusted OR. Our *a priori* confounders were BMI and smoking status. The next step was to fit the conditional logistic regression model including the exposure of interest and the *a priori* confounders. Then we added into the model, one at a time, each of the other potential confounding variables, removing this potential confounder before adding the next. We examined how the OR of the exposure of interest changed as we added each potential confounder. If the inclusion of the confounder changed the effect of the exposure of interest by more than 5% then it was an important confounder and was placed in the fully adjusted model. Missing data for BMI and smoking status were assumed as missing at random and imputed using chained equations. Ten imputations were generated, and the imputed model consisted of all listed confounders, bisphosphonate exposure, and the case-control indicator. Missing data for IMD were assigned a new category. All analyses were undertaken in R v4.0.3 and $P < 0.05$ was considered statistically significant.

Supplementary Table 1. Read and ICD-10 codes used to identify subtrochanteric and femoral shaft fractures.

Readcode	**Description**
S302200	Closed fracture proximal femur, subtrochanteric
S305.00	Subtrochanteric fracture
S310.00	Closed fracture of femur, shaft or unspecified part
S310100	Closed fracture shaft of femur
S314.00	Fracture of shaft of femur
ICD-10 code	**Description**
S72.2	Subtrochanteric fracture
S72.3	femoral shaft fracture

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