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Atypical fractures and bisphosphonate therapy: A cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features

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ABSTRACT

Atypical subtrochanteric/femoral shaft (ST/FS) fractures are increasingly reported in patients on long-term treatment with bisphosphonates (BPs). We estimated the frequency of atypical fractures and their association to BP use in patients aged ≥50 years consecutively admitted to a single center with a new femoral fracture. All individual radiographs were examined and fracture site confirmed. A case–control study of patients with low-energy ST/FS fractures, age- and sex-matched with patients with hip fractures (1:2 ratio), was performed. Patients with atypical ST/FS fractures were further compared with those with ordinary ST/FS fractures. Cortical thickness (CT) was measured in radiographs of cases and controls. Ninety-six of 906 patients (10.6%) had a ST/FS fracture. Of these, 63 with low-energy fractures were individually matched with 126 controls with hip fracture. BPs were used by 9.5% of cases and by 8.7% of controls (OR, 1.10; 95% CI, 0.39–3.06) with comparable duration of therapy between groups (54 ± 35 vs. 54 ± 52 months, $P = 0.53$). CT was comparable between cases and controls, BP users and non-users, and was not related to treatment duration. Atypical fractures were observed in 10/63 ST/FS cases (15.9%). Compared to patients with ordinary ST/FS fractures, those with atypical fractures were using more frequently BPs (OR, 17.0; 95% CI, 2.6–113.3) and glucocorticoids (OR, 5.3; 95% CI, 0.9–28.6). Among patients with atypical fractures, CT was comparable between BP users and non-users. In conclusion, atypical femoral fractures have a low prevalence (1.1% of all femoral fractures), compared to ordinary ST/FS fractures are more frequent in bisphosphonate users, but equally occur in patients never treated with bisphosphonates.

Introduction

Bisphosphonates (BPs) are the mainstay of treatment of osteoporosis, used by millions due to their proven efficacy in reducing fracture risk [1,2]. In recent years case reports and case reviews of rather unusual fractures of the femur below the lesser trochanter (subtrochanteric or femoral shaft) have been reported in patients on long-term BP therapy [3,4]. These fractures have been characterized by a specific radiographic pattern consisting of a simple, transverse or short oblique fracture with unicortical beaking in areas of thickened cortices, and have been designated as atypical [5,6]. The apparent increasing frequency of these fractures, albeit still low in numbers, has attracted the attention of regulatory authorities and of the public at large.

Causality between atypical fractures and BPs is debatable [7–13]. To address this issue we reviewed all radiographs and treatment data from consecutive patients with femur fractures admitted to a single center over an 11-year period with the following specific aims: 1. To estimate the frequency of atypical fractures of the femur. 2. To examine the association between atypical fractures and BPs use. 3. To examine risk factors other than BPs potentially contributing to the risk of atypical fractures.

Methods

Study design

We performed a retrospective analysis of all patients aged ≥50 years consecutively admitted to our Institution for surgical repair of a new fracture of the femur between January 1997 and December 2007. This time frame was selected because alendronate was approved in the Netherlands for the treatment of osteoporosis in 1996. All patients were identified from hospital records using ICD-9-CM discharge codes. Radiographs of all patients were reviewed and fracture site was

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adjudicated and reclassified if not in agreement with the ICD-9-CM coding. A case–control study of all patients with low-energy subtrochanteric or femoral shaft (ST/FS) fractures and patients with hip fractures matched for age and sex in a 1:2 ratio was also performed. Furthermore, we compared patients with atypical fractures of the femur with those with ST/FS fractures without atypical radiographic features within the subset of patients with ST/FS fractures.

Patient identification

The following ICD-9-CM discharge codes were used for the identification of patients with a femur fracture and its specific location: 820.0x, transcervical fracture, closed (including 820.00, 820.01, 820.02, 820.03, and 820.09); 820.2x, pertrochanteric fracture, closed (including 820.20, 820.21, and 820.22); 820.8, unspecified part of the neck of femur, closed; 821.0x, shaft or unspecified part of the femur, closed (including 821.00, and 821.01); 821.2x, lower end, closed (including 821.20, 821.21, 821.22, 821.23, and 821.29). All fractures with ICD-9-CM codes of open fractures (820.1x, 820.3x, 820.9, 821.1x, 821.3x), assumed to be traumatic, were also examined for confirmation of the code and radiographic adjudication. All pathologic fractures, defined by codes 733.10, 733.14, and 733.15, were excluded. We confirmed the validity of the exclusion by evaluating radiographs of a randomly selected subset of patients with these ICD-9-CM codes.

Radiographs of all patients were individually examined and the fracture site identified by the ICD-9-CM code either confirmed or revised. For this, we used the Müller AO Classification of Fractures – Long Bones [14,15]. Subtrochanteric fractures were further defined as fractures occurring within 5 cm distal to the lesser trochanter [5,16]; fractures with an extension to the trochanteric region were not included. Femur fractures were thus classified into 3 groups: hip fractures (including femoral neck and pertrochanteric fractures), subtrochanteric and femoral shaft fractures and lower femur fractures. Only first and new fractures were included.

Case–control study

Cases consisted of all patients with a radiographically confirmed, low-energy-trauma ST/FS fracture. For each case, two age- and gender-matched controls with low-energy hip fractures were randomly selected from the cohort. Low-energy fractures were defined as fractures caused by a fall from standing height or less. Exclusion criteria included non-available radiographs, periprosthetic or high-energy fractures, metastatic bone disease and metabolic bone disease other than osteoporosis.

The following data were collected for all patients: gender, age, previous history of osteoporotic fractures (hip, femur, vertebrae, forearm, humerus and pelvis), past medical history and treatment with glucocorticoids (GCs). Data on type and duration of BP therapy were obtained from hospital records or from the patient's general practitioner. In the Netherlands nearly all individuals are registered with a general practice, independently of health status, and electronic records of all treatments prescribed are available.

Definition of atypical fractures

Radiographs of patients with ST/FS fractures were evaluated by two observers blinded to patients' characteristics and medication use. An atypical fracture was defined as a transverse, or short oblique, non-comminuted ST/FS fracture in an area of thickened cortices with unicortical beaking. The inter-observer kappa coefficient was 0.83.

Cortical thickness

Cortical thickness (CT) was measured from radiographs of cases and controls either just distal to the site of fracture [9], and/or 5 cm below the lesser trochanter by the same observer blinded to patients' characteristics. Values were normalized to bone diameter at the site of measurement to account for differences in magnification. The reproducibility of the measurements was evaluated by triplicate measurements of 14 radiographs at different time points. The coefficient of variation of these measurements was 3.9% and 4.4% for CT just distal to the site of fracture and 5 cm below the lesser trochanter, respectively. This method has limitations, but it is commonly used to measure cortical thickness in cases of femoral fractures [17], including atypical [9].

Statistics

Continuous data are expressed as mean ± standard deviation. Categorical data are reported as numbers and percentages. Taking into account the individual matched case–control design, conditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between ST/FS fractures and potential risk factors. Continuous variables were compared using the independent samples *t* test and ANOVA. Categorical data for unmatched analyses were further analyzed using Fisher's exact test. Correlations were estimated using Pearson or Spearman correlation coefficients. Statistical inferences were made on the basis of a two-sided significance level of $P<.05$. All analyses were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL) and STATA version 8.0 (STATA Corp., College Station, TX).

Results

Patients

Out of 1245 patients with a new fracture of the femur identified by ICD-9-CM discharge codes, 932 were ≥50 years (Fig. 1). Radiographs were available for review in 909 and examination of these radiographs led to exclusion of another 3 patients (one with a fracture of the acetabulum, one with Paget's disease and one with metastatic breast cancer). The final cohort consisted, thus, of 906 patients (29.4% men) with a mean age of 77.9 ± 10.5 years (range 50–99 years). Adjudication of the fracture site by review of individual radiographs of all patients resulted in a different fracture site allocation in 20 patients (2.3%). The final distribution of fracture site after adjudication was as follows: hip 781 (86.2%), ST/FS 96 (10.6%), lower femur 29 (3.2%) and the ratio of hip to ST/SF fractures was 8.1:1. Mean age of the three subgroups was comparable being 78.1 ± 10.3 years in patients with hip fracture, 77.1 ± 12.3 years in patients with ST/FS fracture and 75.3 ± 10.2 years in patients with lower femur fracture (ANOVA, $P=0.30$). There was no significant difference ($P=0.08$) in the distribution of patients according to fracture site during 1997–2002 compared to 2003–2007 (83.8%, 12.5%, 3.6% for hip, ST/FS and lower femur in 1997–2002 and 88.2%, 9.5%, 2.3% for hip, ST/FS and lower femur in 2003–2007).

Case–control study

Of the 96 patients with ST/FS fractures, 33 were excluded from analysis because of high-energy trauma (15), periprosthetic fracture (16), and limited available data due to residence abroad (2). The remaining 63 patients with low-energy ST/FS fractures were individually matched for age and gender with 126 patients with low-energy hip fractures. Of the excluded patients, only one with a periprosthetic shaft fracture used a bisphosphonate (etidronate for 1 year before the fracture). Details of cases and controls are shown in Table 1.

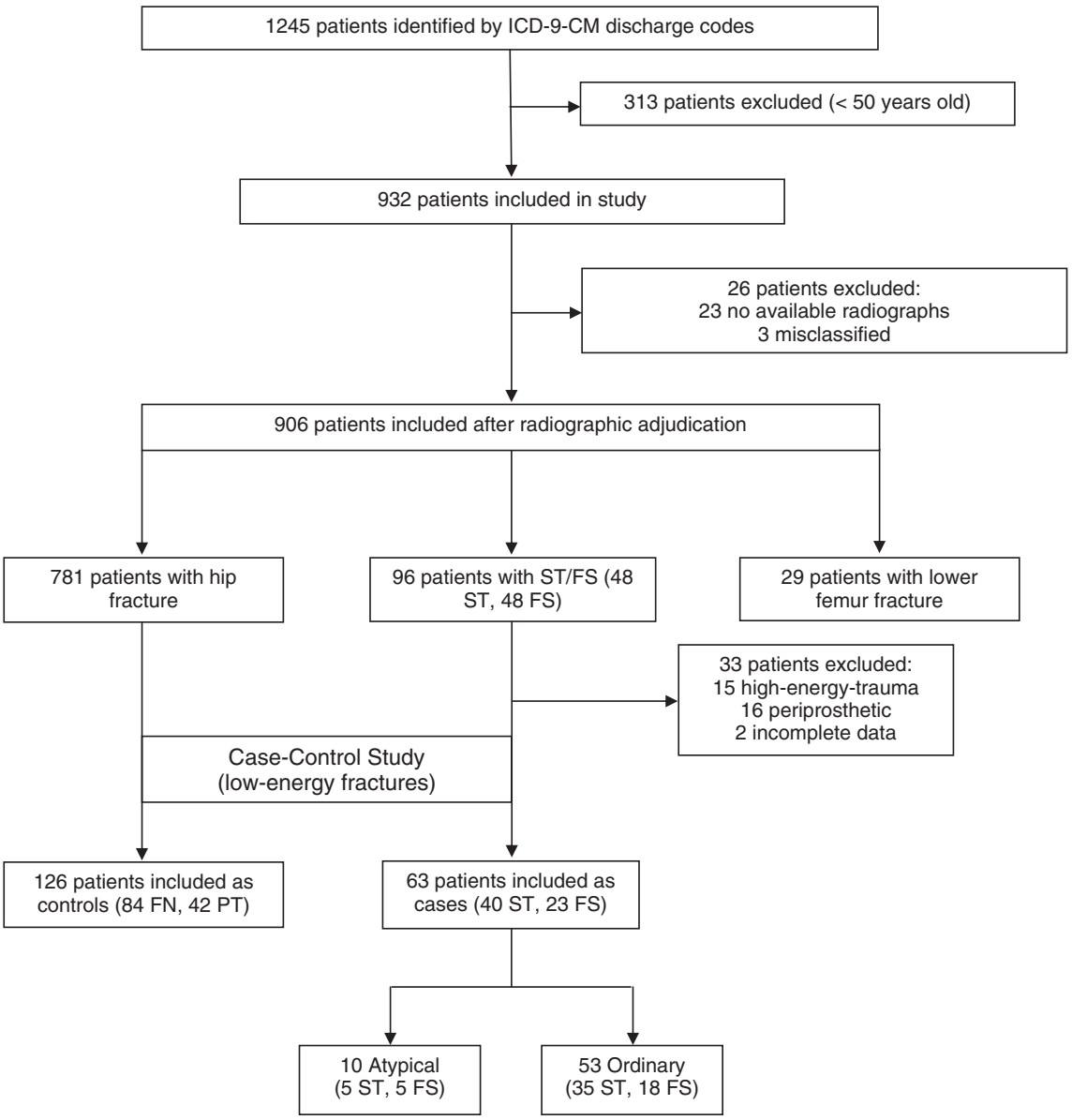

Fig. 1. Flow chart of study subjects with femoral fracture. Abbreviations: ICD-9-CM, International Classification of Diseases, 9th revision, Clinical Modification; ST, subtrochanteric fracture; FS, femoral shaft fracture; FN, femoral neck fracture; PT, pertrochanteric fracture.

At the time of fracture, BPs were used by 9.5% of cases and by 8.7% of controls (OR, 1.10; 95% CI, 0.39–3.06) and the duration of BP use was comparable between the two groups (cases: 54 ± 35 months, controls: 54 ± 52 months, $P = 0.53$) There was no difference in any other characteristic between the two groups, except for the higher prevalence of diabetes in cases (OR, 3.62; 95% CI, 1.45–9.07). The proportion of GCs users was higher and the duration of their use longer albeit non- significantly in the ST/FS group compared to the hip fracture group. There was no significant difference in CT measured 5 cm below the lesser trochanter, between cases and controls (0.41 ± 0.11 vs. 0.40 ± 0.10, $P = 0.71$).

Combining all patients with ST/FS and hip fractures, there was no significant difference in CT between BP users and non-users (0.41 ± 0.13 vs. 0.40 ± 0.10, $P = 0.83$) or between GCs users and non-users (0.42 ± 0.11 vs. 0.40 ± 0.10, $P = 0.48$). There was also no relationship between CT and duration of BPs ($r = 0.028$, $P = .91$) or GCs use ($r = 0.118$, $P = .66$), but the numbers were small. There was, however, a significant negative correlation between CT and age ($r = -0.281$, $P < .001$).

Atypical fractures

Among the 63 patients with ST/FS fractures, we identified 10 patients (15.9%) with radiographic features of an atypical fracture, representing 1.1% of the total cohort. Patients with an atypical fracture were comparable to those with an ordinary ST/FS fracture, except for previous clinical vertebral fractures which were more frequently observed in the former ($P = 0.02$, Table 2). Of the 10 patients with atypical fractures, 4, all women, were treated with a BP at the time of fracture (one etidronate followed by alendronate, two alendronate, one pamidronate) for 3–5 years and two of them were also receiving GCs. These patients accounted for 6.3% of low-energy ST/FS fractures or 0.4% of the total cohort. An additional patient was treated with oral pamidronate for 12 years but had discontinued it 5 years before the fracture. In contrast, only 2 of the 53 patients (OR, 17.00; 95% CI, 2.55–113.26) with an ordinary ST/FS fracture were using BPs (one pamidronate for 10 years and one alendronate for 2 years). There was no difference in the duration of BP treatment between the two groups (Table 2). Representative radiographs of patients with atypical ST/FS

Table 1
Characteristics of subtrochanteric/femoral shaft fracture cases and age- and sex-matched hip fracture controls at admission.

Characteristic	ST/SF Cases ($n=63$)	HF controls ($n=126$)	Odds ratio (95% CI)	*P* value
Age, mean (SD), y	77.1 (12.3)	77.2 (12.3)		NA
Men, no. (%)	12 (19.0%)	24 (19.0%)		NA
Previous fracture, no. (%)	24 (38.1%)	50 (39.7%)	0.94 (0.53–1.69)	.84
Hip	10 (15.9%)	12 (9.5%)	1.71 (0.72–4.06)	.22
Clinical vertebral	8 (12.7%)	19 (15.1%)	0.83 (0.35–1.96)	.67
Distal radius	5 (7.9%)	15 (11.9%)	0.64 (0.22–1.84)	.41
Current BP users, no. (%)	6 (9.5%)	11 (8.7%)	1.10 (0.39–3.06)	.86
Duration BP use*, mean (SD), m	54 (35)	54 (52)		.53
GC users, no. (%)	7 (11.1%)	9 (7.1%)	1.61 (0.58–4.49)	.37
Duration GC use**, mean (SD), m	77 (84)	27 (26)		.11
Rheumatoid arthritis, no. (%)	4 (6.3%)	6 (4.8%)	1.33 (0.38–4.73)	.66
Diabetes, no. (%)	14 (22.2%)	9 (7.1%)	3.62 (1.45–9.07)	.006
Hyperthyroidism, no. (%)	4 (6.3%)	4 (3.2%)	3.00 (0.50–17.95)	.23
CT 5 cm, mean (SD)	0.41 (0.11)	0.40 (0.10)		.71

Abbreviations: ST, subtrochanteric femur fracture; FS, femoral shaft fracture; HF, hip fracture; BP, bisphosphonate; GC, glucocorticoid; CT 5 cm, normalized cortical thickness measured 5 cm below the lesser trochanter; NA, not applicable. * In patients using BP; **In patients using GC.

fractures treated or not with BPs are shown in Fig. 2. A higher proportion of patients with atypical compared to ordinary fractures were treated with GCs (30% vs. 7.5%; OR, 5.25; 95% CI, 0.97–28.55) and for a longer period (160 vs. 15 months) but these differences were not significant.

As expected by the radiographic definition of atypical fractures, patients who sustained these fractures had a significantly higher CT. There was no difference in CT, however, between the patients with atypical fractures treated with a BP (CT just below the fracture, 0.45 ± 0.09; CT 5 cm below the lesser trochanter, 0.51 ± 0.09) compared to those who did not receive BP treatment (CT just below the fracture, 0.44 ± 0.06, $P=.62$; CT 5 cm below the lesser trochanter 0.45 ± 0.10, $P=0.35$).

Discussion

The present study, with adjudication of all radiographs of consecutive patients with femur fractures, was designed to assess the prevalence of atypical fractures and their association to BP use. In our cohort, the characteristics of the patients and the distribution of femur fractures were concordant with those reported in larger epidemiological studies in which ICD discharge codes were used for the identification of the fracture site [10,16]. Miscoding has been previously reported in up to 11% of femoral fractures; [18] this was 2.3% in our cohort. In our study, the prevalence of ST/FS was 10.6% compared to 8% in a similar analysis of the location of femur fractures among millions of individuals ≥50 years identified from the National Hospital Discharge Survey (1996–2006) and from a large medical claims database in the USA [16]. ST/FS fractures occurred more frequently in women than in men, and their frequency increased with age being 2.8/100 patients in patients aged 50–64 years and 5.8/100 in those aged ≥80 years, also in agreement with previous data [16]. Furthermore, cortical thickness, as measured in our study, decreased with age, as expected by the pathophysiology of age-related bone loss. Our cohort is, therefore, representative of elderly patients with fractures of the femur. In addition, the percentage of patients with ST/FS fractures using BPs and glucocorticoids was also similar to those reported by Abrahamsen et al. in a much larger Danish cohort (9.5 vs. 7% and 11.1% vs. 9.6%, respectively) [10].

Our data show that low-energy atypical femur fractures represent 1.1% of all femur fractures, 10.4% of all ST/FS fractures and 15.9% of low-energy ST/FS fractures. Atypical fractures occurring in patients treated with BPs accounted for 0.4% of all femur fractures and 6.3% of

Table 2
Characteristics of patients with subtrochanteric and femoral shaft fracture according to the presence or absence of the atypical radiographic pattern.

Characteristic	Atypical ST/SF ($n=10$)	ST/FS ($n=53$)	Odds ratio (95% CI)	*P* value
Age, mean (SD), y	73.0 (15.3)	77.9 (11.7)		.35
Men, no. (%)	1 (10.0%)	11 (20.8%)		.67
Subtrochanteric fracture, No. (%)	5 (50.0%)	35 (66.0%)		.48
Previous fracture, no. (%)	5 (50.0%)	19 (35.8%)	1.79 (0.46–6.98)	.49
Hip	1 (10.0%)	9 (17.0%)	0.54 (0.06–4.84)	.69
Clinical vertebral	4 (40.0%)	4 (7.5%)	8.17 (1.61–41.46)	.02
Distal radius	2 (20.0%)	3 (5.7%)	4.17 (0.60–28.96)	.18
Current BP users, no. (%)	4 (40.0%)	2 (3.8%)	17.00 (2.55–113.26)	.004
Duration BP use*, mean m	45	72		.76
GC users, no. (%)	3 (30.0%)	4 (7.5%)	5.25 (0.97–28.55)	.06
Duration GC use**, mean (SD), m	160 (57)	15 (6)		.06
Rheumatoid arthritis, no. (%)	1 (10.0%)	3 (5.7%)	1.85 (0.17–19.85)	.51
Diabetes, no. (%)	2 (20.0%)	12 (22.6%)	0.85 (0.16–4.57)	.85
Hyperthyroidism, no. (%)	2 (20.0%)	2 (3.8%)	6.38 (0.78–51.90)	.12
CT below fracture, mean (SD)	0.45 (0.07)	0.34 (0.13)		.02
CT 5 cm, mean (SD)	0.48 (0.10)	0.39 (0.10)		.03

Abbreviations: ST, subtrochanteric femur fracture; FS, femoral shaft fracture; BP, bisphosphonate; GC, glucocorticoid; CT below fracture, normalized cortical thickness measured just distal to the site of fracture; CT 5 cm, normalized cortical thickness measured 5 cm below the lesser trochanter. * In patients using BP; **In patients using GC.

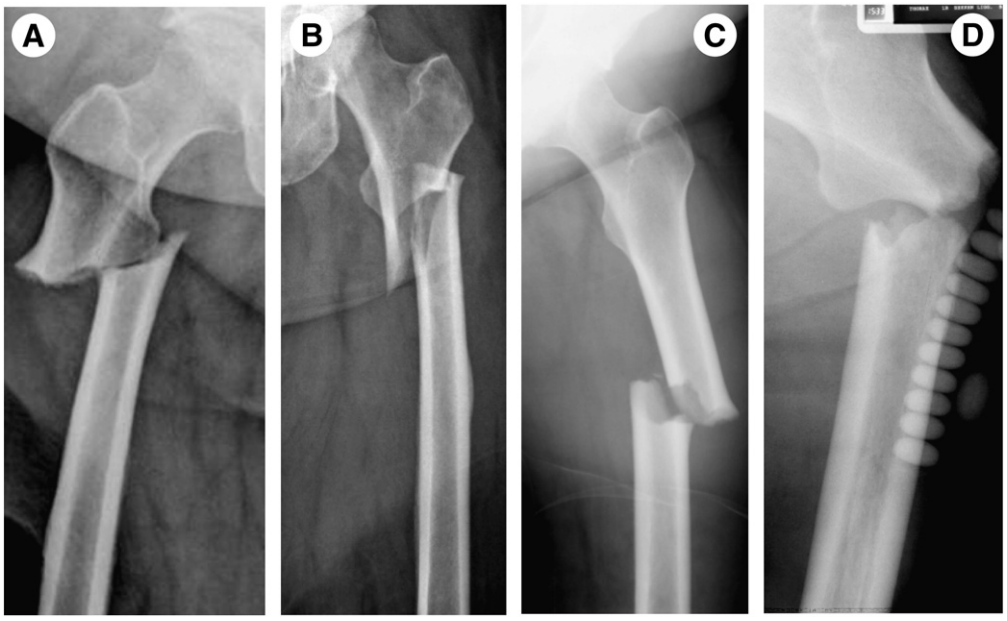

Fig. 2. Representative radiographs of patients with atypical subtrochanteric (ST) and femoral shaft (FS) fractures treated or not with bisphosphonates: A) and B) atypical ST fractures in patients treated with bisphosphonates; C) atypical FS occurred in a patient who had discontinued pamidronate 5 years before the fracture; D) atypical ST in a man who has never been treated with a bisphosphonate.

low-energy ST/FS fractures. The data indicate that atypical fractures of the femur are infrequent, occurring in 1:100 patients with femur fractures and in 1:10 patients with ST/FS fractures.

Use of BPs has been implicated in the pathogenesis of atypical fractures of the femur [5,6,9,11,19,20]. An increasing number of patients with atypical fractures on long-term BP therapy is being reported but a causal association has not yet been established [3,4,7,12,13]. An association between BPs treatment and atypical fractures has not been documented in cohort studies or in clinical trials [7,8,10,21], but no radiographs were available in these studies for the recognition of the radiographic pattern thought to be characteristic of atypical fractures. This is also illustrated in our case–control study in which we found no difference in the use of BPs between patients with low-energy ST/FS fractures and patients with hip fractures. This finding is in keeping with that of Abrahamsen et al. [10] but at odds with the case–control study of Lenart et al. [9] who reported a higher proportion of BP users among patients with ST/FS fractures compared to those with hip fractures. There are, however, differences in study design between our study and that of Lenart et al. [9], the most important in that study being the lack of information about the population from which these cases were selected, the inclusion of only women and the exclusion of patients receiving treatments which might affect bone fragility, such as GCs. These differences do not allow direct comparison of results. In addition, we found no increase in the frequency of ST/FS fractures over an 11-year period starting 1 year after the approval of alendronate for the treatment of osteoporosis in the Netherlands. Based on the data from of our case–control study we could conclude that there is no association between ST/FS fractures and BP use, as also previously reported [10]. However, because of the availability of radiographs in all studied patients we were able to identify patients with atypical fractures among those with ST/FS fractures and to compare them to patients with ordinary ST/FS fractures. This comparison revealed that BPs were used much more frequently by patients with atypical fractures (40%) compared to those with the more common ordinary ST/FS fractures (3.8%). This finding is in agreement with that of other studies and may suggest an association between BPs use and atypical fractures [9,11]. However, we also found that about half of patients with atypical fractures were not using BPs indicating that factors other than BPs are highly likely to be involved in their pathogenesis. Low-energy fractures of the femur with the characteristic radiographic pattern of atypical fractures have been previously reported in patients not receiving BPs [9,22–26]. Our results show that the frequency of such fractures is 0.6% of all femur fractures. Schilcher and Aspenberg [24] used a national data base of drug dispension and estimated that the incidence density of atypical femur fractures was 0.02/1000 per year in untreated women being considerably higher (1/1000 per year) in women treated with BP.

One of the radiographic characteristics of atypical fractures is the thickening of the femoral cortex. Although a generalized increase in cortical thickness of the diaphysis is currently considered a minor feature of atypical femoral fractures [27] we did not encounter any atypical fracture without cortical thickening. It has been postulated that this cortical thickening is due to long-term BP use, which reduces bone remodeling and increases secondary mineralization of bone [20,28], but we previously argued that this may not be a plausible explanation [4]. In support of this, is our finding of 5/10 patients with atypical fractures who were never treated with BP as was also the case in 3/13 patients reported by Lenart et al. [9]. Moreover, we show that cortical thickness is not different in patients with atypical fractures with or without BP therapy and that cortical thickness does not increase with time on BPs, strongly supporting the notion that thick cortices are not the result of BP therapy. It may rather be that patients with thick cortices are at increased risk of an atypical fracture and that BPs may contribute to this risk. This hypothesis remains, however, to be tested.

A further interesting finding of our study is the possible contribution of glucocorticoid therapy to the risk of atypical fractures. Use of these agents has emerged as an important risk factor for atypical fractures in Caucasian women treated with BPs and the data reported here are in line with these observations [4]. Thirty percent of all patients with atypical fractures were using GCs for a much longer period of time compared to only 7.5% of those with ordinary ST/FS fractures, a difference just missing statistical significance. This association warrants further investigation in larger cohorts.

Our study has limitations: it is a single center study and although the data are comparable to those of other epidemiological studies, we do not know whether they can be extrapolated to the whole population of patients with fractures of the femur; the number of

atypical fractures is rather low and it was not possible to document stress ST/FS fractures, which have also been reported in patients receiving BPs [4], as these patients are usually not admitted to hospital. However, compared to previously reported data, our study has a number of strengths: we included both men and women with no selection bias over an 11-year period; radiographs of all patients were reviewed and reclassified when required, and treatment history was reliably documented in all patients.

In conclusion, atypical femoral fractures have a low frequency, compared to ordinary ST/FS fractures are more frequent in bisphosphonate users, but equally occur in patients never treated with bisphosphonates.

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