J Bone Miner Metab (2017) 35:562–570
DOI 10.1007/s00774-016-0790-7

ORIGINAL ARTICLE

Atypical femoral fractures in Italy: a retrospective analysis in a large urban emergency department during a 7-year period (2007–2013)

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Received: 11 July 2016 / Accepted: 20 September 2016 / Published online: 9 November 2016

Abstract The aim of this study was to determine the incidence of atypical femoral fractures (AFFs) seen in a large emergency department in Italy. It was a retrospective study of all men and women aged 40 years or older admitted to the Emergency Department of Parma University Hospital for a femoral fracture. Cases were identified in the hospital database with use of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 820 or 821 or text strings. All the radiographic images of fractures not clearly identified as proximal or condylar were retrieved and evaluated by three independent reviewers. Fractures were considered as atypical if all three reviewers agreed on at least four of five major features defined by the 2013 American Society for Bone and Mineral Research criteria. In the 7-year period (2007–2013), with a total follow-up of 1,383,154 patient-years, we found 22 AFFs in 21 patients, accounting for 7.1% of low-trauma subtrochanteric/femoral shaft fractures and 0.6% of all femoral fractures. The incidence was very low (1.6 in 100,000 patient-years in both sexes combined). In contrast, the incidence of classic fractures of the proximal end of the femur was at least two orders of magnitude higher (typical/atypical rate ratio 152). Bisphosphonate use was reported in 13 patients (62%; mean treatment duration 9 years; range 5–14 years). Among 286 patients with typical subtrochanteric/femoral shaft fractures, 20 were being treated with bisphosphonate (7%; odds ratio 22; 95% confidence interval 8–58; $p < 0.001$). This study confirms the very low incidence of AFFs in the largest Italian cohort of patients to date. Even though the risk is higher in patients treated with bisphosphonates, AFFs are very rare, and typical femoral fractures are at least 100-fold more frequent.

Keywords Atypical femoral fractures · Bisphosphonates · Osteoporosis · Epidemiology

Introduction

Atypical femoral fractures (AFFs) are rare low-energy fractures located in the subtrochanteric and diaphyseal region of the femur and characterized by unique radiographic characteristics, such as a transverse fracture line originating in the lateral cortex and periosteal or endosteal thickening at the fracture site. The diagnosis of AFF specifically excludes high-trauma fractures, fractures involving the femoral neck or the trochanteric region, pathological fractures associated with cancer or other bone diseases, and periprosthetic fractures [1–3].

In recent years, interest in AFFs has substantially increased because they have emerged as potential complications of long-term antiresorptive therapies (bisphosphonates and denosumab), which are most commonly used to treat patients with osteoporosis [3]. Even though they also occur in patients not exposed to these drugs, evidence for

Electronic supplementary material The online version of this article (doi:10.1007/s00774-016-0790-7) contains supplementary material, which is available to authorized users.

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an association between antiresorptives and AFF has continued to accumulate in recent years and is considered quite robust [3].

To clearly delineate the features that distinguish AFFs from ordinary osteoporotic femur fractures the American Society for Bone and Mineral Research (ASBMR) Task Force on Atypical Femoral Fractures developed a first set of diagnostic criteria in 2010 [2], and a revised case definition in 2013 [3]. AFFs are considered as a form of stress or insufficiency fracture, which occur "along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare." The updated version requires that at least four of five major features must be present: minimal or no trauma; substantially transverse or short oblique orientation; medial spike in complete fractures and involvement of the lateral cortex in incomplete fractures; no or minimal comminution; localized periosteal or endosteal thickening of the lateral cortex at the fracture site. Minor features sometimes associated with these fractures (generalized increase in cortical thickness of the femoral diaphysis, prodromal symptoms, bilateral incomplete or complete femoral diaphysis fractures, delayed fracture healing) are not required for the diagnosis [3].

Radiographic adjudication is necessary for the recognition of AFFs. Since 2009 several studies have examined the epidemiology of AFFs with radiographic adjudication, but in different populations and with nonuniform diagnostic criteria. As a result, there are some differences in the prevalence and incidence rates of AFFs. The reported proportion of subtrochanteric/femoral shaft (ST/FS) fractures with atypical features ranges from 1 to 48%, whereas the overall incidence, even though consistently very low, ranges from about 1 in 100,000 person-years to 113 in 100,000 person-years in long-term bisphosphonate users [3, 4].

Italian epidemiological data on the frequency of AFFs are limited. The largest retrospective radiological study [5] included 319 femoral fractures and identified two cases of atypical fractures in a 2-year period (0.6% of all femoral fracture, 5% of the ST/FS fractures). Other reports include a study on risk factors for the development of AFFs in 11 women with AFFs receiving long-term oral bisphosphonate therapy [6] and isolated case descriptions [7, 8].

This study was undertaken to obtain a more precise estimate of the frequency of AFFs by applying retrospectively the revised ASBMR criteria on femoral fractures observed in 7-year period (2007–2013) in the emergency department of a large referral hospital in Italy.

Materials and methods

This is a retrospective study of all men and women admitted to the Emergency Department of Parma University Hospital for a femoral fracture over a period of 7 years (2007–2013).

Parma University Hospital, a 1250-bed teaching general hospital, is the main hospital in the province of Parma (in Emilia-Romagna, Italy) and serves a well-defined catchment area with a population of approximately 345,000 (about 80% of the whole province). The hospital is a level 2 trauma center, and in our area all individuals with known or suspected hip fractures are referred to the Emergency Department. The records of all patients seen in the Emergency Department are stored in an electronic database, containing demographic and clinical data. X-ray reports and images have also been available through the hospital intranet since 2007.

Data on all patients aged 40 years or older seen in the Emergency Department with a potential femoral fracture between January 1, 2007 and December 31, 2013 were retrieved from the electronic database of the hospital with use of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 820 or 821 or the terms femor* AND fratt* to include all possible variants of the Italian terms for femur and fracture. The extracted records were then reviewed to confirm the presence of the fracture at the time of the visit.

To identify the exact fracture location, the Emergency Department admission summary and the X-ray report were examined regardless of sex, trauma energy, or clinical notes to avoid possible biases in the selection of the images. Fractures clearly identified as cervical, trochanteric, or condylar (concordant Emergency Department admission summary and X-ray report) were excluded from further analysis. All the radiographic images of the other fractures (including those described as subtrochanteric or diaphyseal or those with an unclear site because of an incomplete description) were retrieved. The images were labeled with a numeric anonymous code and saved in a PDF file for evaluation by three independent reviewers (M.P., A.G., and G.G.), blind to all demographic, clinical, or therapeutic information.

In the first phase, only the revised ASBMR major radiographic criteria were evaluated, regardless of trauma or clinical information [3]. Fractures occurring along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare were assessed for the presence of (1) transverse or short oblique orientation, (2) localized periosteal or endosteal thickening of the lateral cortex, (3) involvement of the lateral cortex in incomplete fractures or medial spike in complete fractures, and (4) comminution. Fractures involving the femoral neck or the trochanteric region, condylar fractures, pathological fractures associated with cancer or other bone diseases, and periprosthetic fractures were excluded. After two rounds of independent work several weeks apart, a final meeting of all three evaluators was

held to resolve the remaining doubts and for the definitive adjudication, taking into account the fracture circumstances to exclude high-energy injuries not due to minimal or no trauma or a fall from a standing height. Fractures were considered as atypical if all three reviewers agreed on at least four of five major features defined by the revised ASBMR criteria regardless of the presence or absence of minor features [3].

Clinical data and exposure to bisphosphonates were captured from the notes in the Emergency Department medical record; the duration of bisphosphonate use was calculated from the self-reported initial year of therapy.

The results are presented as absolute frequencies, percentages, and rates for 100,000 person-years; confidence intervals (CIs) were computed with Wilson's approximation for percentages and Byar's approximation for rates [9]. For incidence calculation, population data were obtained from the county registers. The 7-year average population was used as the population at risk. For the comparison between the groups with atypical or typical fracture, the Mann–Whitney test was used for continuous variables (age) and the two-tailed Fisher exact test was used for categorical variables (sex). The odds ratio for bisphosphonate exposure and its CI were computed by standard methods [10].

The study was performed in accord with the Declaration of Helsinki, under the terms of the relevant local legislation.

Results

The initial search on the records in which reference was made to a femoral fracture retrieved 4781 visits to the Emergency Department among patients aged 40 years or older. Of these, 778 visits were excluded not because of the fracture itself, but because of lack of follow-up, complications, or unrelated health problems in patients with a previous fracture of the femur, leaving 4003 confirmed femoral fractures. The clinical and X-ray reports clearly identified 3519 proximal fractures (cervical or trochanteric; 3335 due to low-energy trauma) and 39 condylar fractures of the distal end of the femur, whereas 445 were described as involving the subtrochanteric region or the diaphysis of the femur. After exclusion of fractures involving the trochanteric region or below the supracondylar flare, and periprosthetic, high-energy trauma and pathological fractures, the final set comprised 308 confirmed ST/FS fractures due to low-energy trauma (Fig. 1). All patients were Caucasian.

Among the 308 ST/FS fractures, 22 met the major ASBMR criteria in 21 patients (19 women, 2 men); one

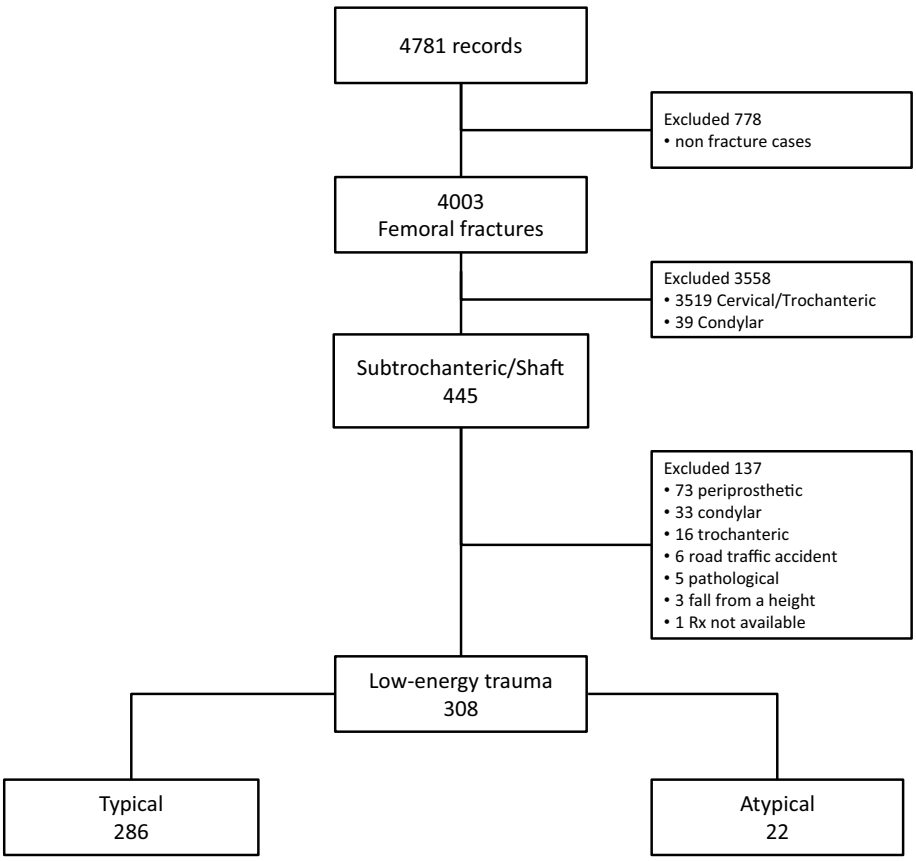

Fig. 1 Flowchart describing the identification of atypical fractures of the subtrochanteric and femoral shaft area in the study population

woman had a contralateral AFF 6 years after the first one (see the electronic supplementary material). AFFs accounted for 7.1% of fragility ST/FS fractures (95% CI 4.8–10.6%) and 0.6% of all femoral fractures (95% CI 0.4–0.9%). No fracture was formally reported as an atypical or stress fracture by the radiologist. In all cases, the contralateral side was not screened.

The median age of the patients was 72 years (interquartile range 68–79 years). In five cases no previous trauma was reported, whereas in the other cases the fracture was associated with a simple fall; in two cases a spontaneous fracture was considered as the cause of the fall.

Bisphosphonate use was reported in 13 of 21 patients (62%; 95% CI 41–79%) and for 14 of 22 fractures (64%; 95% CI 43–80%). Except for one woman who had received monthly infusions of zoledronic acid for treatment of metastatic breast cancer for 3–4 years (the exact duration was unclear), all the other patients (12 patients,13 fractures) had been treated for osteoporosis. The duration of bisphosphonate therapy, essentially based on patients' recall, was difficult to determine in some cases. However, 12 patients had been treated for 5 years or more (mean treatment duration 9 years; range 5–14 years); the duration was unknown in two cases. Six patients had been treated with alendronate alone, whereas the others had switched between different bisphosphonates, including alendronate, risedronate, ibandronate, clodronate, and neridronate. Two patients continued bisphosphonate use after the fracture; one developed a new complete contralateral AFF in 2013 (Fig. 2), and one was found to have an incomplete contralateral atypical fracture in 2014 (after the end of the observation period of the study), 6 years after the first one in both cases. Two previously untreated women began bisphosphonate therapy (alendronate and ibandronate) after the fracture.

Previous fractures were reported in three patients (two vertebral, one humeral); one woman with an AFF due to a fall had a simultaneous fracture of the wrist. Three patients had the concomitant presence of rheumatoid arthritis treated with glucocorticoids and steroid-induced diabetes. One woman had Parkinson's disease and one woman had chronic obstructive pulmonary disease (Table 1).

Patients with typical ST/FS fractures were older (median age 83.5 years; interquartile range 77–88 years) than patients with AFFs (median age 72 years; interquartile range 68–79 years; $p < 0.001$). Women accounted for 80% of typical ST/FS fractures and 90% of AFFs; this difference was not statistically significant ($p = 0.39$). Among 286 patients with typical ST/FS fractures, 20 were being treated with bisphosphonates (7%). Exposure to bisphosphonates was significantly more frequent in patients with AFFs than in the group with typical fractures (62% vs 7%; odds ratio: 22; 95% CI 8–58; $p < 0.001$).

Patients with typical proximal fractures were also older (median age 84.0 years; interquartile range 77–88 years; $p < 0.001$) and predominantly female (74%). The sex distribution difference was not significantly different ($p = 0.09$).

Since the catchment area of the Emergency Department is well defined, it was possible to derive the incidence of AFFs, with use of the average 7-year population

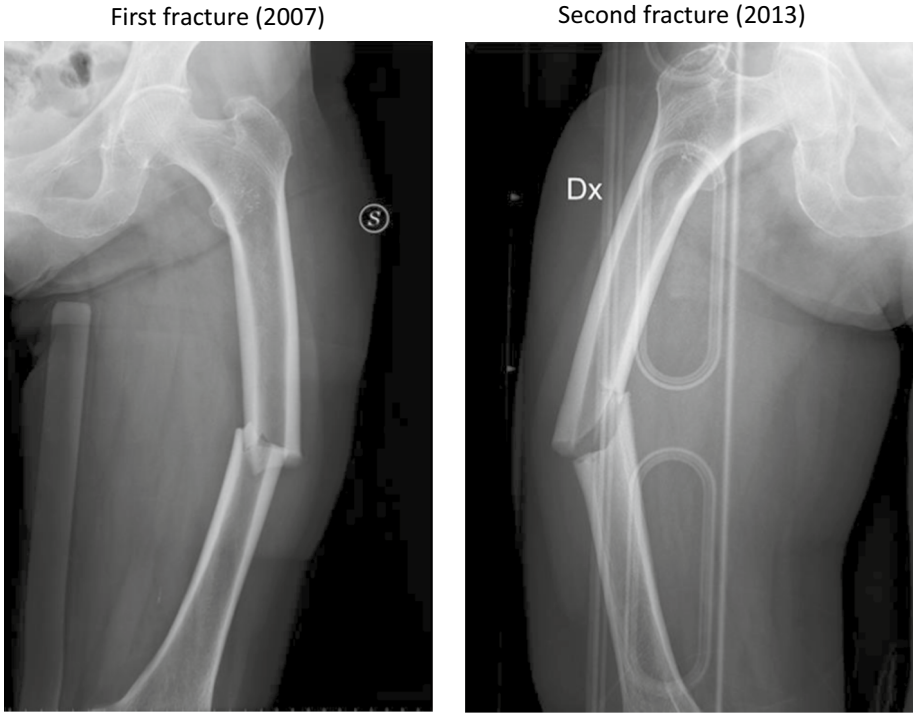

Fig. 2 Double atypical femoral fracture in a woman treated with alendronate. The first fracture (2007), after 8 years of treatment, was not recognized as atypical, and alendronate therapy was continued. After the second fracture (2013), alendronate therapy was suspended and teriparatide therapy was initiated

Table 1 Clinical data of the 21 patients

Patient	Sex	Age (years)	Trauma	BP treatment	BP treatment duration (years)	Previous fractures	Rheumatoid arthritis	Diabetes	Glucocorticoid treatment	COPD	Parkinson's disease
1	F	59	Spontaneous	No	–	No	No	No	No	No	No
2	F	69	Simple fall	Yes	10	No	No	No	No	No	No
3	F	76	Spontaneous	No	–	No	No	No	No	No	Yes
4	F	72	Simple fall	No	–	No	No	No	No	No	No
5	M	79	Spontaneous	No	–	No	No	No	No	No	No
6	F	84	Simple fall	Yes	Unknown	No	Yes	No	Yes	No	No
7	F	65	Simple fall	Yes	10	No	No	No	No	No	No
8	F	69	Simple fall	No	–	No	No	No	No	No	No
9	F	85	Spontaneous	Yes	Unknown	No	No	No	No	No	No
10	F	70	Spontaneous	Yes	6	No	No	No	No	No	No
11	M	51	Simple fall	No	–	No	No	No	No	No	No
12	F	76	Simple fall	No	–	Humerus	No	Yes	No	Yes	No
13	F	79	Simple fall	Yes	7	No	No	No	No	No	No
14	F	79	Spontaneous	Yes	6	No	No	No	No	No	No
15	F	57	Simple fall	Yes	7	No	Yes	Yes	Yes	No	No
16	F	68	Simple fall	Yes	5	No	No	No	No	No	No
17	F	63	Simple fall	Yes	14	No	No	No	No	No	No
18	F	87	Simple fall	No	–	Vertebrae	No	No	No	No	No
19	F	71	Spontaneous	Yes	6	No	Yes	Yes	Yes	No	No
20	F	72	Simple fall	Yes	4	No	No	No	No	No	No
21	F	77	Simple fall	Yes	8	Vertebrae	No	No	No	No	No

BP bisphosphonate, *COPD* chronic obstructive pulmonary disease, *F* female, *M* male

of individuals aged 40 years or older. The incidence in both sexes combined was 1.6 in 100,000 person-years (95% CI 1.0–2.4). The incidence was significantly higher in women (2.7 in 100,000 person-years; 95% CI 1.7–4.1) than in men (0.3 in 100,000 person-years; 95% CI 0.1–1.0). In the same period there were 2515 women and 820 men with typical proximal fractures due to low-energy trauma. The incidence was 241 in 100,000 person-years in both sexes combined (340 in 100,000 person-years in women and 127 in 100,000 person-years in men), resulting in incidence rate ratios of 152 (95% CI 100–242), 126 (95% CI 81–206), and 410 (95% CI 113–3391) respectively.

Discussion

To the best of our knowledge, this is the largest Italian study on the frequency of AFFs and the first using the most recent ASBMR 2013 criteria.

In a 7-year period we found 22 AFFs in 21 patients, accounting for 7.1% of low-trauma ST/FS fractures and 0.6% of all femoral fractures. The estimated absolute incidence was very low (1.6 in 100,000 patient-years in both sexes combined, 2.7 in 100,000 patient-years in women, and 0.3 in 100,000 patient-years in men). In contrast, the incidence of classic fractures of the proximal end of the femur was at least two orders of magnitude higher (241 in 100,000 patient-years; with a typical/atypical rate ratio of 152).

The diagnosis of AFF requires the recognition of a specific radiographic pattern. Several studies with radiographic adjudication of AFFs have been published in recent years [5, 11–25].

The percentage of ST/FS fractures considered atypical is widely different, ranging from 1 to 48% [3]. Incidence estimates in the general population range from less than 1 in 100,000 patient-years to 10 in 100,000 patient-years, with significantly higher values in individuals exposed to bisphosphonates, depending on the treatment duration (up to 113 in 100,000 patient years in patients treated for 8 years or more) [3, 4].

A comparison among different reports is not straightforward because of differences in the methods and in the populations examined.

Many surveys used different approaches for the identification of ST/FS fractures [International Classification of Diseases, Ninth Revision (ICD-9) or International Classification of Diseases, Tenth Revision (ICD-10) codes or coding specific for the database], for the diagnosis of AFF (2010 or 2013 ASBMR criteria or other slightly different criteria) and for adjudication (single assessor, many independent assessors, or consensus between two or more evaluators).

The populations examined differ in sex distribution, age range, and race/ethnicity composition. In particular, race/ethnicity is an increasingly recognized risk factor for AFF [1, 15, 17, 26]. In a recent prospective study, the relative hazard for AFF adjusted for age, bisphosphonate therapy duration, and current use of bisphosphonates was 6.6-fold higher in Asian women than in white women [27]. Since Asians were overrepresented in several US studies, contributing from 25% [26] to 49% [15] of identified AFF cases, the prevalence of Asians in the different studies may significantly impact the epidemiological results.

Despite some divergence in the results, in most studies AFFs account for about 5–15% of ST/FS fractures and only a minor fraction of the total femoral fractures (0.5–1%). Incidence estimates in the general population range from about 1 in 100,000 patient-years to 10 in 100,000 patient-years. Our results are within the lower range of these estimates (Table 2), but as explained above, a direct comparison with other studies is not possible.

Long-term bisphosphonate exposure (mean 9 years; range 5–14 years) was observed in 62% of patients with AFFs. In published studies, the prevalence of bisphosphonate use in patients with atypical fractures ranges from 42% [20] to 97% [26]. Although this may be due to different distributions of risk factors or frequency of bisphosphonate use in the diverse populations, the radiographic criteria may modify the adjudication of AFF [15, 16, 28]. For example, the reclassification according to the revised ASBMR criteria increased the number of nonusers classified as having atypical fractures and resulted in a decrease of the estimated relative risk from 47% to 19%, suggesting that the ASBMR criteria may be less specific for bisphosphonate use [28].

As observed in this study, AFFs can occur in bisphosphonate-naïve patients [4]. However, a significant association between AFF and bisphosphonates has been consistently reported in most epidemiological studies with radiographic review, although the strength of the association differs. In agreement with these results, in our study the odds of being treated with bisphosphonate was 22-fold higher in patients with AFF as compared with patients with typical ST/FS fractures.

Even though observational studies cannot establish causal relationships, the evidence linking long-term treatment with bisphosphonates with AFF is convincing [3] and the risk appears to increase with the duration of bisphosphonate exposure [15].

It has been hypothesized that the long-term reduction of skeletal remodeling induced by bisphosphonates might predispose to AFF by compromising the mechanical properties of bone. However, this is not proven, and other short-term effects of bisphosphonate are likely [29]. The current consensus is that AFFs are stress or insufficiency fractures

Table 2 Frequency of atypical femoral fractures (*AFFs*) in the general population in published reports with radiographic adjudication and in the present study

Study	Country	Years	Frequency of AFFs among ST/FS fractures (%)[a]	Incidence (100,000 patient years)[a]
Lenart et al. [11]	USA	2000–2007	32 (20–47)[b]	–
Girgis et al. [12]	Australia	2003–2008	13 (9–19)	–
Giusti et al. [13]	Netherlands	1997–2007	16 (9– 27)	–
Schilcher et al. [14]	Sweden	2008	5 (4–6)	3.9 (3.0–5.0)
Dell et al. [15]	USA	2007–2011	3 (3–4)	11.0
Feldstein et al. [16]	USA	1996–2009	38 (32–45)	5.9 (4.6–7.4)
Lo et al. [26]	USA	2007–2008	48 (37–59)	–
Meier et al. [17]	Switzerland	1999–2010	8 (6–11)	3.2
Thompson et al. [18]	UK	2008–2010	7 (5 –10)	–
Warren et al. [19]	New Zealand	2003–2008	8 (4–17)	–
Beaudouin-Bazire et al. [20]	France	2005–2010	4 (2–7)	–
Shkolnikova et al. [21]	Australia	2007–2012	30 (21–42)	–
Luangkittikong and Unnanuntana [23]	Thailand	2002–2013	6 (4–8)	–
Saita et al. [24]	Japan	2005–2010	4 (2–7)	–
Juby et al. [22]	Canada	2002–2013	12 (9–16)	1.4 (0.8–2.5)
Bottai et al. [5]	Italy	2011–2013	5 (1–17)	–
Schilcher et al. [28]	Sweden	2008–2010	15 (13–18)	5.9 (5.1–6.9)
Mahjoub et al. [25]	Canada	2009–2010	18 (13–24)	7.0 (4.7–9.3)
Present study	Italy	2007–2013	7 (5–11)	1.6 (1.0–2.4)

ST/FS subtrochanteric/femoral shaft

[a] The 95% confidence interval is given in *parentheses*.

[b] Based on ten AFFs in bisphosphonate-treated patients and three AFFs in untreated patients

that develop over time [3]. The lateral cortex of the femur is exposed to high tensile stress during each step. The lower limb geometry, the pattern of activity, and the musculoskeletal architecture of the individual may predispose to localized stress microdamage. Circulating bisphosphonates localize in these areas, and suppression of targeted intracortical remodeling at this site could impair the normal healing process, leading to crack propagation beyond a point of no return and eventually to fracture [3, 29]. The hypothesis of inhibition of targeted remodeling is supported by the observation that the risk of atypical fractures decreases rapidly after cessation of bisphosphonate treatment [28].

Nevertheless, the incidence of typical, low-energy fractures of the proximal end of the femur is much higher than that of AFFs (at least 100-fold in our study). Since bisphosphonates can substantially reduce the incidence of typical hip fractures, the balance between the benefits of treatment and harm caused by treatment remains clearly positive, especially during the first 3–5 years.

Consistent with previous reports [4], patients with AAF were younger than those with typical ST/FS or proximal fractures and were almost exclusively women (90%). Even though the sex distribution was not significantly different from that observed for typical fractures in this study, perhaps because of limited statistical power, other reports have found a higher risk of AFFs in women not explained by differences in prescription rates or age and possibly related to anatomical differences that increase the stress in the lateral femoral cortex and therefore susceptibility to fatigue fracture [30].

In accordance with the ASBMR criteria, periprosthetic fractures were excluded. However some peri-implant fractures exhibit simple transverse orientation, lateral cortical thickening, and lack of comminution consistent with atypical features [31]. Further revisions of the diagnostic criteria may address this issue.

It is worth noting that no fracture was described or classified as atypical in the radiological reports. Since the recognition of established fractures or cortical changes indicative of AFFs is critical for the proper treatment of patients, a wider application of radiological guidelines is clearly important for clinicians [32].

The study has several strengths. The capture of ST/FS fractures was virtually complete since all patients with known or suspected hip fractures in a well-defined catchment area are referred to the Emergency Department. Moreover, femoral fractures were retrieved not only by International Classification of Diseases codes

but also by a textual search in the clinical and radiological records. All available radiographs of the identified cases were reviewed and AFFs were adjudicated by three independent assessors, with a final consensus meeting. The latest ASMBR task force criteria were applied. In the 7-year period, about 4000 femoral fractures were observed, and the sample size, though predictably smaller than that of nationwide or multicenter surveys, is relatively large and in the top half of sample sizes of the available studies.

The study also has limitations. The records contained only succinct clinical data, and we had no information on several confounding variables, bone mineral density, vitamin D status, bone turnover markers, or risk factors for fracture or metabolic bone disease. Likewise, information about the ASBMR minor criteria (e.g., prodromal symptoms, frequently preceding AFFs [33]) was incomplete, but this is not required for diagnosis. The available radiographs were acquired in an emergency setting, and the patient positioning was not always optimal, making adjudication difficult in a few cases. Bilateral views were often not available, and the contralateral femur was not assessed. The duration of bisphosphonate use was obtained by self-report and was unknown in two cases; however, this does not compromise the frequency and rate estimates. The 7-year period is too short to detect reliable time trends in the incidence of AFFs.

In conclusion, in the largest Italian study to date using the most recent ASBMR criteria (2013), we observed a very low incidence of AFFs. Although the risk was higher in patients treated with bisphosphonates, typical low-energy femoral fractures were at least 100-fold more frequent. Even though the available reports agree on the rarity of AFFs, in the different studies there is a certain degree of heterogeneity in the percentage of ST/FS fractures considered atypical, their incidence in the general population, and the proportion of bisphosphonate users among patients with AFFs. Our results are within the lower range of the published estimates and may add new information on the epidemiology of AFFs. Since no fracture was formally reported as atypical by the radiologist, it is imperative to improve the radiological reporting.

Acknowledgement We thank Daniele Santilli, rheumatologist, for informing us of the patient who developed the second incomplete atypical femoral fracture in 2014, after the end of the observation period of the study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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