Bisphosphonates have been proven to decrease the fracture risk when used in the recommended indications, such as postmenopausal osteoporosis [1–3]. Nevertheless, concern about potential side effects related to diminished bone turnover has never abated since their introduction four decades ago. Several findings have added to the uneasiness, such as the identification of microcracks of uncertain clinical significance and the occurrence of jaw osteonecrosis in cancer patients receiving high-dose bisphosphonate therapy. Reports of atypical femoral fractures in patients on bisphosphonate therapy have generated both considerable interest and major anxiety as a possible clinical manifestation of the old and unproven “frozen bone” concept, in which treatment-induced suppression of bone turnover is believed to decrease bone strength.

1. Lessons from studies of radiologically confirmed cases

A 2005 paper reports nine cases of spontaneous nonvertebral fractures in alendronate-treated patients, including 3 diaphyseal femoral fractures [4]. Imaging studies showed delayed or absent healing and histomorphometry findings indicated bone turnover inhibition with no double labeling, suggesting a treatment effect that was either too strong or too long lasting. Furthermore, the features of these fractures were reminiscent of the lesions seen in osteomalacia related to phosphate wasting or in diseases characterized by low bone turnover rates (e.g., hypophosphatasia and pycnodysostosis). Subsequently, several case-reports and small case-series studies were published (list in [5]), as well as a systematic analysis of 141 published cases [6]. What lessons can we draw from these data?

First, the histomorphometry findings do not clearly support treatment-induced bone turnover inhibition as the only mechanism underlying atypical femoral fractures. In the 57 cases with histomorphometry studies of bone from the fracture site or transtibial biopsy specimens [5], the findings varied widely. A decrease in bone formation was found in most but not all cases. This decrease was marked in some patients but was not accompanied with mineralization disorders, and increased resorption was observed occasionally [5–7]. In addition, the occurrence of atypical femoral fractures after less than 3 years of bisphosphonate exposure in 25% of cases, with a median of 60 months and a range of 3 to 192 months [6], does not support a role for excessively prolonged bone turnover inhibition. Thus, a vast spectrum of situations has been encountered.

The reported cases have allowed the identification of several distinctive features of atypical femoral fractures [8]. A task force of the American Society for Bone and Mineral Research (ASBMR) defined diagnostic criteria to improve the recognition and incidence assessment of atypical femoral fractures (Table 1) [5]. The case definition excludes femoral neck fractures, intertrochanteric fractures extending to the subtrochanteric region, periprosthetic fractures, and fractures related to bone tumors. All the major criteria are required by the case definition. These criteria include the location of the fracture under the lesser trochanter and above the femoral condyles. In addition, the fracture line must be transverse or only slightly oblique, with no commin-
tion. The fracture may be confined to the lateral cortex or extend across the bone from one cortex to the other, with or without a medial cortical beak. A periosteal reaction along the lateral cortex is among the minor criteria that are not required for the diagnosis, together with cortical thickening, which is a controversial sign [6,9]. Similarly, co-morbidities and concomitant treatments are considered to be risk factors that are not required for the diagnosis. Treatments associated with atypical femoral fractures consist of glucocorticoids, proton pump inhibitors, and bisphosphonates.

In a retrospective case-control study of postmenopausal women who underwent surgery in a single center between 2000 and 2007 for low-energy femoral fractures, the 41 cases with subtrochanteric/diaphyseal fractures were compared to 82 matched controls with intertrochanteric/femoral neck fractures [10]. Bisphosphonate exposure was more common among the cases (15/41) than among the controls (9/82), the odds ratio (OR) was 4.44 with a 95% confidence interval (95% CI) of 1.77–11.35 (P = 0.002). Of the 15 cases exposed to bisphosphonates, 10 had the radiographic features of atypical femoral fractures. In a Swedish cohort of 3087 bisphosphonate-exposed women older than 55 years [11], five atypical femoral fractures meeting predefined criteria [10] occurred over an 18-month period, 3.5 to 8.5 years after bisphosphonate therapy initiation, yielding an incidence density of 1/1000 per year (95% CI, 0.3–2.0). Although the incidence density was low in absolute terms, it was considerably higher than in the 88,869 same-age women who were not exposed to bisphosphonates, among whom only three sustained atypical femoral fractures. In a literature review that identified 87 cases of atypical femoral fractures in bisphosphonate-exposed women, about 10% of patients had co-morbidities such as rheumatoid arthritis, chronic obstructive pulmonary disease, asthma, or diabetes, nearly one-fourth had a history of systemic glucocorticoid therapy, and more than one-third used proton pump inhibitors [6].

2. Additional information from registries

An abundance of epidemiological information has been obtained from registries that distinguish proximal femoral fractures from subtrochanteric or diaphyseal fractures. Possible coding mistakes constitute a limitation inherent in the registry method. In addition, atypical femoral fractures meeting ASBMR criteria may account for only about 10% of subtrochanteric and diaphyseal fractures [6], which in turn account for about 10% of all femoral fractures. The extent to which these percentages may be affected by parameters such as bisphosphonate exposure is unknown. Although these limitations should be borne in mind, registries supply useful information on several issues.

A cross-sectional study of 11,944 patients entered in the Danish registry between 1997 and 2005 showed that only 7% of the patients with subtrochanteric fractures were exposed to alendronate, a percentage identical to that among patients with proximal femoral fractures [12]. In contrast, almost twice as many patients had a history of glucocorticoid exposure in the group with subtrochanteric fractures compared to the group with proximal femoral fractures. A matched control analysis of the registry data compared 5187 alendronate-exposed patients to 10,374 unexposed patients with subtrochanteric fractures. After adjustment for co-morbidities, the hazard ratio (HR) for subtrochanteric fractures in alendronate-exposed patients was 1.46 (95% CI, 0.91–2.35; P = 0.12), which was similar to the value in the group with proximal femoral fractures (HR, 1.45; 95% CI, 1.21–1.74; P < 0.001).

In an analysis of healthcare utilization data from the US, subtrochanteric and diaphyseal femoral fractures were uncommon, with only 104 cases among 33,815 patients treated with bisphosphonates, raloxifene, or calcitonin [13]. The incidence rate in the bisphosphonate-exposed group was 1.46/1000 patient-years (95% CI, 1.11–1.88), which was not significantly different from the incidence rate in the group exposed to raloxifene or calcitonin (1.43/1000 patient-years; 95% CI, 1.06–1.89). Similarly, a post hoc analysis of data from three randomized trials of bisphosphonate therapy for postmenopausal osteoporosis (the Fracture Intervention Trial [FIT], FIT Long-Term Extension Trial [FLEX], and Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly trial [HORIZON]) identified only 12 subtrochanteric or diaphyseal femoral fractures in 10 patients among the 14,195 study patients [14], yielding a rate of 2.3/10,000 patient-years. Compared to the placebo group, the relative hazard in the intervention group was 1.03 (95% CI, 0.06–16.46) in FIT (alendronate for 4 years), 1.33 (95% CI, 0.12–14.67) in FLEX (alendronate for 10 years) and 1.5 (95% CI, 0.25–9.0) in HORIZON (zoledronic acid for 3 years). Although these data are of interest, radiographs were rarely available for review and the atypical nature of the fractures was therefore usually left unconfirmed. In addition, the exposure duration of less than 4 years in most cases and use of low alendronate dosages in some patients cast further doubt on the relevance of the findings.

The above-mentioned Danish registry was used for a considerably larger study of 103,562 bisphosphonate-exposed patients and 310,683 unexposed controls followed up from 1996 to 2006 [15]. Interestingly, this study compared the risk of subtrochanteric and diaphyseal femoral fractures before and after exposure to

### Table 1

<table>
<thead>
<tr>
<th>Diagnostic criteria for atypical femoral fractures (Task force of the American Society for Bone and Mineral Research) [5].</th>
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<tr>
<td><strong>Major criteria</strong></td>
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<tr>
<td>Proximal fracture line under the lesser trochanter and distal fracture line above the femoral condyles</td>
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<tr>
<td>No trauma or low-energy trauma</td>
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<tr>
<td>Transverse or only slightly oblique fracture line (angle &lt; 30°)</td>
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<tr>
<td>Noncomminuted fracture</td>
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<tr>
<td>Complete fracture crossing from one cortex to the other, with or without a medial cortical beak OR Incomplete fracture (or fissure) involving only the outer cortex</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
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<tr>
<td>Periosteal reaction along the lateral cortex</td>
</tr>
<tr>
<td>Increased cortical thickness</td>
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<tr>
<td>Predromic aching pain in the groin or thigh</td>
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<tr>
<td>Bilateral fracture</td>
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<tr>
<td>Delayed healing</td>
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<tr>
<td>Co-morbidities: rheumatoid arthritis, vitamin D deficiency, hypophosphatemia, or other</td>
</tr>
<tr>
<td>Concomitant treatments: bisphosphonates, glucocorticoids, proton pump inhibitors</td>
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</table>

**Exclusion criteria**

Femoral neck fracture, intertrochanteric fractures with extension to the subtrochanteric femur, periprosthetic fracture, pathological fracture related to a primary bone tumor or bone metastasis

N.B. The diagnosis requires the presence of all the major criteria. None of the minor criteria is required, but minor criteria may be present concomitantly with major criteria.
osteoporosis medications. The risk increased after the initiation of alendronate (HR, 2.41; 95% CI, 1.78–3.27) or etidronate (HR, 1.96; 95% CI, 1.62–2.36) but not after the initiation of raloxifene (HR, 1.06; 95% CI, 0.34–3.32). Importantly, before treatment initiation, the risk was increased not only in the groups given alendronate (OR, 2.36; 95% CI, 2.05–2.72) or etidronate (OR, 3.05; 95% CI, 2.59–3.58), but also in those given raloxifene (OR, 1.90; 95% CI, 1.07–3.40) or strontium ranelate (OR, 2.97; 95% CI, 1.07–8.27). These data suggest a possible role for the underlying bone disease in the occurrence of atypical fractures, with a further risk increase if bisphosphonates are used.

Registy data can also serve to assess the potential link between the risk of subtrochanteric or diaphyseal femoral fractures and the duration of drug exposure. The healthcare utilization database study from the US contained little information about patients exposed to bisphosphonates for longer than 5 years, and the confidence interval was therefore extremely wide in this group (incidence rate/1000 patient-years, 2.02; 95% CI, 0.41–10) [13]. In the Danish registry of alendronate-treated patients, 39 proximal femoral fractures and five subtrochanteric fractures were identified among the 178 patients treated for more than 6 years and having adherence rates of 80% or more [12]. Compared to 356 untreated controls, these 178 patients had no long-term elevations in the risks of proximal femoral fractures (HR, 1.24; 95% CI, 0.6–2.34) or subtrochanteric fractures (HR, 1.37; 95% CI, 0.22–8.62). The same Danish registry was used for a larger cohort study of 39,567 patients who started alendronate therapy between January 1996 and December 2005 and who were compared to 158,268 age- and sex-matched untreated controls. The risk of subtrochanteric or diaphyseal femoral fractures was not significantly different between the patients treated for 9 years (highest quartile) and those treated for 3 months (lowest quartile) [16].

Registy data provide an overall picture of medications used to prevent osteoporotic fractures. They indicate that the risk/benefit ratio of osteoporosis medications is extremely favorable over time. A Swedish registry identified 6409 cases of low-energy diaphyseal femoral fractures over 7 years [17]. No effort was made to differentiate typical and atypical fractures. The annual incidence was 10/100,000 person-years and remained stable between 1998 and 2004. Follow-up data from the Study of Osteoporosis that enrolled 9704 women older than 65 years between 1986 and 1988 [18] showed that 1396 femoral fractures occurred over more than 23 years, including 45 (less than 2%) subtrochanteric fractures. The incidence of subtrochanteric fractures increased with age to the same extent as the incidence of proximal femoral fractures. In the US, a study of hospital discharge data showed a decrease in admissions for hip fractures from 600/100,000 to 400/100,000 person-years between 1996 and 2006 with no change in the incidence of subtrochanteric and diaphyseal femoral fractures (less than 20/100,000 person-years in women) [19]. A just-published study of two large databases in the US showed that the age-adjusted rate of typical hip fractures decreased by 31.6% in women (from 1020.5 to 697.4/100,000 population) and 20.5% in men (from 424.9 to 337.6 per 100,000 population) [20]. In contrast, the age-adjusted rates of subtrochanteric fractures remained unchanged in men and increased by 20.4% in women, from 28.4/100,000 population in 1999 to 34.2/100,000 population in 2007. During the same period, bisphosphonate use increased chiefly in women, from 3.5% to 16.6%, whereas only 2.3% of men were using bisphosphonates in 2007. In terms of the crude risk/benefit ratio, these age-adjusted data show that over the last decade in this population, the prevention of 100 typical hip fractures was associated with only one additional subtrochanteric fracture.

Another study released this year used two medical claims databases from 2001 to 2008 in the US [21]. Oral bisphosphonate therapy was started in 460,584 women older than 45 years, in whom mean follow-up was 2.4 years. In this large study population, the fracture incidence decreased with increasing adherence as assessed using the medication possession ratio (MPR). Thus, in patients aged 65 years or older, the fracture incidence was 5.12% in the group with MPR values lower than 50% and 3.75% in the group with MPR values of 50% or more. Extrapolating these numbers to the overall population of women treated with oral bisphosphonates in the US suggests more than 27.9 million patient-years of exposure with MPR values of 50% or more and the prevention of 144,670 fractures.

3. Lessons for clinical practice

Although atypical femoral fractures are uncommon, a complaint of thigh pain from a patient at risk for osteoporosis should suggest this possibility, particularly if the patient has a history of bisphosphonate exposure. The time interval from the onset of prodromic pain and the diagnosis of an atypical femoral fracture varies widely, from 1 week to 2 years [6]. The index of suspicion should be particularly high in patients with rheumatoid arthritis, chronic obstructive pulmonary disease, asthma, or diabetes; and in those with a history of exposure to systemic glucocorticoid therapy or proton pump inhibitors. Recurrences have been reported in patients who had several of these risk factors [6].

Radionuclide bone scanning combined with single-photon emission computed tomography may help in the early diagnosis of bone fragility heralding a fracture, particularly when uptake is increased at the contralateral and apparently healthy femur, consistent with a stress fracture [7]. In contrast, it seems that neither bone marker levels [5] nor bone mineral density values [6] are of diagnostic assistance.

4. Conclusion

Although both the existence of atypical femoral fractures and the major role for bisphosphonate therapy as a risk factor have been firmly established, these fractures account for only a small proportion of subtrochanteric and diaphyseal femoral fractures and are about 100 times less common than proximal femoral fractures. Therefore, the risk of atypical femoral fractures does not call into question the extremely favorable risk/benefit ratio of bisphosphate therapy in patients with osteoporosis. The number of fractures prevented by bisphosphate therapy far exceeds the number of fractures potentially related to bisphosphonates. Further studies are needed to elucidate the mechanisms underlying atypical femoral fractures, with the goal of developing preventive strategies.

Disclosure of interest

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B Cortet: Honoraria as an expert or lecturer for Amgen, Daiichi-Sankyo, Ferring, Lilly, MSD, Medtronic, Novartis, Roche, Servier, and Warner & Chilcott; financial support for research projects or as an investigator in studies sponsored by Amgen, Lilly, MSD, Novartis, Roche.

T Thomas: Honoraria as an expert or lecturer for Amgen, Daiichi-Sankyo, BMS, GSK, Lilly, Merck, Novartis, Roche, Servier, Warner & Chilcott; financial support for research projects or as an investigator in studies sponsored by Amgen, Chugai, Lilly, Merck, Pfizer, Roche, Servier, and Warner & Chilcott.

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