Atypical Femur Fractures: 81 Individual Personal Histories

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Context: An online voluntary association of individuals who had incurred one or more atypical femur fractures (AFFs) while taking bisphosphonates for prevention or treatment of osteoporosis provided an opportunity to collect long-term histories.

Setting: Individuals from a nationwide general community completed an anonymous survey documenting their history.

Participants: Within a larger cadre, cases were selected where the documentation, including fracture radiographs, verified the diagnosis based on published standards. Eighty-one of this group responded to the anonymous survey.

Interventions: We describe passively collected observational data only.

Outcome Measures: The incidence of a large number of potential variations was determined.

Results: The mean duration of bisphosphonate treatment was 9.5 yr. Prevention was the initial indication in 68% of the subjects; 94% started on alendronate, 77% reported prodromal pain, only 16% of these were diagnosed with incident stress fractures, and 39.5% experienced a contralateral AFF from less than 1 month to 49 months after the first. Of 71 subjects with a completed first AFF, 38% reported delayed healing, 11% had a complete contralateral AFF, and 22% underwent prophylactic rodding for a contralateral stress AFF. Forty-four percent of subjects with complete AFFs were continued on a bisphosphonate after the fracture. Thirty-five percent incurred a metatarsal fracture.

Conclusions: AFF patients experienced delayed healing, prodromal pain, and persisting risk of a contralateral and/or other fracture. Femur pain evaluation in patients on long-term bisphosphonates may facilitate early diagnosis of stress AFFs, permitting intervention, thus reducing completed and/or contralateral or other fracture risk. The details of these histories will assist in counseling regarding prognosis after an initial AFF. (J Clin Endocrinol Metab 97: 4324–4328, 2012)
reported that among women treated with a BP for at least 5 yr, the risk of subtrochanteric or femoral shaft fractures was approximately 1 in 500 or 0.2% (5). Given the widespread international use of BPs, even this relatively small risk represents a large and increasing number of cases.

We believe that the availability and assessment of more longitudinal individual histories is required before clinicians faced with providing an estimate of prognosis after such fractures can offer data-based answers. Such material has not been easy to assess, given the absence of any registry.

**Subjects and Methods**

The American Society for Bone and Mineral Research (ASBMR) Task Force (3) on atypical subtrochanteric and diaphyseal femoral fractures (AFFs) considered both complete and incomplete (insufficiency) cases. Several years ago, the corresponding author of this paper began an online support group for patients with AFFs who had contacted her seeking additional information. Documentation consistent with an AFF was required for admission to the group. We have had an opportunity to assess long-term clinical outcomes extending over an interval of 7 yr in a group of more than 145 persons who had been prescribed BP medications for an initial dual-energy x-ray absorptiometry-based indication for treatment of osteoporosis or the prevention of osteoporosis (due to a diagnosis of osteopenia), and who incurred atypical femur low-impact fractures. Our assessment has permitted some limited conclusions to be made regarding practice patterns and the prognosis in the 2003–2011 interval. This cadre is larger than any similar series yet described in the literature. It is comprised of individuals who voluntarily contacted the corresponding author in search of a source of information in addition to that provided by their attending physicians. Data contribution from the complete collection of more than 145 persons is continuing.

The present report describes 81 individuals out of the larger number with sufficient information, including radiographs that provide satisfactory confirmation of the nature of their fracture, who responded to an anonymous questionnaire. The radiographs and reports were independently evaluated by two physician authors, an internist, and a gynecologist. Most of the adjudicated images were additionally accompanied by confirmatory reports from an attending radiologist, although these reports all preceded wide dissemination of the consensus definitions. In the 81 cases, which represented all of the individuals who provided complete responses, we found consistency with the definition of an AFF, with the proviso that four cases involved limited comminution of complete fractures in the same clinical setting as the remaining 77. We included these individuals because we strongly feel that the restriction of the AFF definition reached by the ASBMR Task Force (3) to noncommminuted fractures excludes many cases that clearly deserve consideration. It is understood that the inclusion of comminuted fractures in the usual post hoc treatment-blinded medical record analysis review is fraught with opportunity for misjudgment, but we agree with the Medicines & Health Products Regulatory Agency (UK) (www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON120213) and the European Medicines Agency (www.ema.europa.eu/ema/index.jsp; Documents WC50011711.pdf and WC500127478.pdf) in demoting this mandatory “major feature” to an optional status, at least when considering cases in which the treatment status is known. Our four included cases met the criteria of the ASBMR Task Force in all other particulars.

The survey we used included documentation of demographic definitions, BP use, contralateral fractures, delayed healing, prodromal pain, and long-term outcomes. It is important to recognize that this survey does not afford information regarding the incidence of AFFs and may be biased by a possible tendency of patients with complicated clinical courses to have been more motivated to seek contact with the corresponding author, who had previously published case reports illustrative of this problem. More details of the population reported are given in Table 1.

**Results**

In the 81 cases reported here, the fractures were distributed over an interval of 11 yr. The dates of the 71 first complete fractures were as follows: 2001 (two cases), 2002 (two cases), 2004 (one case), 2005 (one case), 2007 (three cases), 2008 (14 cases), 2009 (20 cases), 2010 (24 cases), and 2011 (four cases through mid-year). No cases commencing after July 10, 2011, are included. The distribution of these patient-initiated contacts may be related to the popular press coverage of the atypical fractures in the later years. Of 78 women and three men, the first or only femur fracture was complete in 71 (mean age when fractured, 64.5 yr; range, 43.5–82), whereas 10 had a stress fracture (mean age when fractured, 68.0 yr; range, 57–89).

Fifty-five of the 71 with completed fractures (77%) reported prodromal pain (for a mean of 9.4 months before fracture; range, 1–24), but only nine of these were diagnosed as an incident stress (insufficiency) fracture before sustaining a complete fracture. These nine stress fractures had been treated conservatively, and the time between that diagnosis and the subsequent complete fracture ranged from 1 to 24 months (mean, 9.4 months), with the longer duration occurring at the end of the series.
from a few days to 3 yr. Sixty-one patients had sought treatment for persistent thigh, leg, or hip pain and had multiple studies and procedures that did not discover the problem. Studies included x-rays of the leg and x-rays, computed tomography, or magnetic resonance imaging (MRI) of the back, hip, or knee; procedures included lumbar steroid injections, knee arthroscopy, knee replacement, and lumbar spine surgery. None of these interventions led to resolution of the pain, which presumably had been caused by an unrecognized stress fracture of the femur because complete fractures ensued.

The details of the 10 fractures initially diagnosed as stress fractures are: six were rodded after intervals of as little as a few hours to up to 5 months after the initial diagnosis; and none of the four who were conservatively treated went on to completion up to the time of the survey closure.

For the 71 fractures initially diagnosed when they were complete, the mean duration of prior BP treatment was 9.15 yr (range, 1.5–15). For the 10 with an initially diagnosed stress fracture, this was 9.10 yr (range, 6–12). Prevention of osteoporosis (T-score above −2.5) was the initial indication for medication in 68%. None of the patients were being treated for metastatic malignant disease. Ninety-four percent were initially on alendronate, but others had taken only risedronate or zoledronic acid. Of patients begun on alendronate after a diagnosis of osteopenia, 94.9% (37 of 39) had been prescribed the 10 mg/d or 70 mg/wk treatment dose.

Thirty-two of the 81 patients (39.6%) also experienced a contralateral AFF from less than 1 month to 49 months after the first AFF, with a mean interval of 10.2 months. Those who incurred a contralateral AFF (stress or complete) included 50% of the patients whose first AFF never fractured completely. Seven of the 81 patients were still taking a BP at the time the second AFF was diagnosed. Three of the seven (43%) who continued the BP after the first AFF fractured the second femur more than 12 months after the first—at 13, 26, and 30 months; four of 24 (17%) who stopped at the time of the first fracture sustained a second one beyond 1 yr—at 13, 17, 17, and 24 months.

Of the 71 with a completed first AFF, 38% reported delayed healing. This was partially qualitative information, based upon the opinions received from their surgeons. However, 27 of the responses included quantitative information; the minimum time for healing in this group was 6 months, and the mean was 13.5 months. We received answers to this section of the survey from only four of the six initially stress-fractured and rodded cases. These four reported that healing was not delayed.

Thirty-five percent of the entire group developed a metatarsal fracture during or after BP treatment, two of

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### TABLE 2. BP use

| Duration of BP use before initially diagnosed complete AFF (n = 71) | 9.15 yr (range, 1.5–15) |
| Duration of BP use before initially diagnosed stress AFF (n = 10) | 9.10 yr (range, 6–12) |
| BP initially prescribed for prevention based on a diagnosis of osteopenia | 68% (53/78) |
| Alendronate (Fosamax) initially prescribed | 94% (76/81) |
| Risedronate (Actonel) initially prescribed | 5% (4/81) |
| Zoledronic acid initially prescribed for bone loss, not metastatic disease | 1 |
| Respondents prescribed 2 BPs | 27 |
| Respondents prescribed 3 BPs | 3 |
| Initial alendronate dose prescribed for prevention was 10 mg/d or 70 mg/wk | 66% (50/76) |
| Continued on BP after initially diagnosed complete AFF | 44% (31/71) |
| Still on BP at time of contralateral stress fracture or AFF | 34% (11/32) |
| Continued BP after bilateral complete AFF | 2 |

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### TABLE 3. Atypical fracture history

| Initially diagnosed fracture was complete | 87.7% (71/81) |
| Initially diagnosed fracture was a stress fracture | 12.3% (10/81) |
| Prodromal pain preceded initially diagnosed complete fracture | 77% (55/71) |
| Mean duration prodromal pain before initially diagnosed fracture | 9.4 months (range, 1–24) |
| Stress fracture initially diagnosed before complete fracture | 13% (9/71) |
| Bilateral stress and/or complete fractures | 39.6% (32/81) |
| Initially diagnosed stress fracture was treated conservatively (not rodded) | 4/10 |

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which the FDA granted approval of the drugs. We hope manufacturers in the pivotal trials providing the basis upon ment for longer than the period studied by the manu-
effect, although the relative risk of different BPs is un-
but this is yet to be determined. AFFs appear to be a class 
techniques from a patient who sustained an AFF after 
point, and others used another BP exclusively—risedro-
in our survey were switched to another BP at some 
that is Food and Drug Administration (FDA)-approved 
agnosis of osteopenia rather than osteoporosis, and 
limitations of the use of the drugs in this setting. 
Delayed healing was found to be very common among 
the repaired fractures (38%), a finding that has been re-
ported in other studies as well. In their review of data of 
141 women published in 31 case series/reports, Giusti et al. (11) found delayed healing in 38.3%.

Our clinical findings are similar to those of 102 femur 
fracture cases from Kaiser Permanente with typical radio-
logical features of AFFs: 70% of that group had prodro-
mal pain (as did 77% of our group of completed first 
fractures), and 25% (compared with 36% of ours) had 
either a complete or stress fracture of the contralateral 
femur (8). Data from large health maintenance organiza-
ations provide an alternative approach to long-term follow-
up, but there is no guarantee that all initially treated pa-
tients will remain within the system.

Our study reconfirms the acknowledged importance 
(3, 12, 13) of evaluating long-term BP patients with un-
explained thigh or hip pain for prevalent insufficiency fractures; early diagnosis of stress AFFs permits medical or surgical intervention, thus reducing the completed fracture risk. Patients with one AFF, whether a stress or a completed fracture, have a significant risk of sustaining a contralateral AFF (36% in this study), and this risk persists for years after stopping the BP. Continuation of BP treatment after an AFF occurs prolongs the risk of a second 
AFF, as was also recently reported by Dell et al. (14). 
Examples in our larger group reveal that even as recently as mid-2012, some physicians still advised patients to con-
tinue taking their BP even after an AFF, unaware that this is likely to increase the risk of a second AFF and of delayed healing. The FDA in their Oct 2010 advisory (10) recommend stopping BPs after an AFF occurs. We hope that this information will be more widely disseminated so that more complete fractures can be prevented.

The finding that only 10 of the 40 contralateral 
fractures in our study were complete fractures reflects the fact that most of the remaining patients underwent prophylactic rodding of the second femur after a stress fracture was diagnosed in the second femur. After an AFF of the first leg, the contralateral femur should be assessed (usu-
ally with a bone scan or MRI) for a stress fracture. The inadequacy of the radiographic plain film in this context has been cited by many authors, who, based on their clinical experience in diagnosing atypical femur stress fractures, recommend follow-up of negative plain films with a bone scan or MRI (13, 15). The authors of a recent review of 17 personally managed atypical BP-associated femoral stress fractures concur, noting that with plain x-rays, “the stress fracture line is obscured unless a near-perfect radiographic projection is ob-
tained,” whereas “MRI scans reveal the stress fracture lines with surrounding edema” (16).

Patients with stress or complete AFFs also risk delayed healing. It is noteworthy that 23% of the patients with completed initially diagnosed fractures reported no prodromal pain; screening of asymptomatic BP users for greater than 3 yr has been reported (17) to reveal an unsuspected 2% rate of prevalent insufficiency fractures.

Our observation of 34.6% occurrence of metatarsal fractures during or after BP use suggests that AFFs alone do not comprise the full scope of the potential fractures associated with BP use. There is accumulating evidence, largely limited to case reports of an association between BP therapy and fractures of other high-stress bones such as the metatarsals (6), pelvic girdle, and ribs (2), and the tibia (18). The present data enlarge the scope of the potential association with cortical highly stressed bones in addition to the femur, and we hope to be able to expand further on this connection as more confirmed data become available on more of our cases. Any future surveys will include attention to any systematic association of concomitant fractures such as we have seen with the metatarsals.

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