

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: 0000–0000, 2012)

Acquired fragility of bone associated with bisphosphonate (BP) medication was observed *in vivo* in experimental studies in 2000 (1) and was first described in humans in 2003 (2). The problem has recently attracted patient concern, scientific evaluation (3), and regulatory scrutiny (4). Well-designed database reviews (5) have provided some potential information about rates, and case reports (6) have described the subsequent clinical course of

one or several individuals, but little information about postfracture long-term outcomes has been available in the medical literature. Conclusions reached by database reviews taking into account duration of therapy and using retrospective radiograph evaluation (7) have often been at odds with others not including radiograph examination. A recent epidemiological study that separated long-term BP users from the majority who take BPs for shorter periods

ISSN Print 0021-972X ISSN Online 1945-7197

Printed in U.S.A.

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doi: 10.1210/jc.2012–2590 Received June 24, 2012. Accepted September 24, 2012.

Abbreviations: AFF, Atypical femur fracture; BP, bisphosphonate; MRI, magnetic resonance imaging.

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 the 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 noncomminuted 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/

TABLE 1. Patient demographics

| | |
|--|------------------------|
| Gender | 78 women, 3 men |
| Median age (n = 71) at initially diagnosed complete fracture | 64 yr (range, 43.5–82) |
| Median age (n = 10) at initially diagnosed stress fracture | 68 yr (range, 57–89) |
| Median age (n = 81) at the time of survey closure mid-2011 | 67 yr (range, 53–92) |
| Ever a smoker | 2.5% (2/81) |
| Regular prednisone (or equivalent) use | 7.4% (6/81) |
| Estrogen replacement therapy | 47% (37/78) |
| Reported physical activity level before fracture | |
| Low | 3.7% |
| Average | 34.6% |
| Somewhat greater than average | 30.7% |
| Much greater than average | 21.0% |

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 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

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 |

the 81 patients sustained a fracture of a bone in the pelvis, and three developed concurrent osteonecrosis of the jaw. There were also metatarsal fractures reported that preceded the femoral break.

Our results are summarized in Tables 2, 3, and 4.

Discussion

We recognize that our described method of data collection is not typical of chart-based retrospective reviews. However, we believe that in many cases the patient may be able to provide a continuous personal story that exists only in part in any individual medical chart. Despite the possibility of a bias toward the more complicated cases, this group illustrates the potential range of antecedents and sequelae of an AFF. Outlier cases are clearly useful in describing the possible prognosis to a patient. The present study was

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 |

TABLE 4. Atypical fracture outcome

| | |
|--|---------------|
| Delayed union of first complete fracture (see <i>Results</i>) | 38% (27/71) |
| Portion with delayed union requiring additional surgery to promote union | 63% (17/27) |
| Portion of initial complete fractures followed by a complete contralateral fracture | 13% (9/71) |
| Portion of initial complete fractures having contralateral prophylactic rodding | 25% (18/71) |
| Portion of all 81 patients who underwent surgery on both femurs | 33% (27/81) |
| Portion of 10 initial unilateral stress fractures subsequently having bilateral stress fractures | 50% (5/10) |
| Initial rodded stress fracture followed by rodding of a contralateral stress fracture | 40% (4/10) |
| Portion of all initially diagnosed fractures who stopped BP by that time or within 3 months and later incurred a second femoral fracture | 35.5% (22/62) |
| Portion of all initially diagnosed fractures who did not stop BP and later incurred a second femoral fracture | 52.6% (10/19) |
| Metatarsal fracture occurred during or after BP treatment | 34.6% (28/81) |
| Stress or complete fracture of a bone in the pelvis (n = 2) | 2.5% |
| Osteonecrosis of the jaw (n = 3) | 3.7% |

limited to patients with AFFs known to have used one or more BPs, so it differs from case comparison studies and is not intended to suggest AFF rates. One study (8), which included records of all the health maintenance organization patients with AFFs, reported finding that 95% had been on a BP. Another study (9) of all the admissions to a major hospital over an 11-yr interval found that 82% of the patients with fractures with the atypical features had a history of BP treatment compared with 6% of the much larger group with “classic” (non-atypical) characteristics. This Swiss study used the ASBMR definition of atypia (3).

The majority of patients in our study were put on a BP after a dual-energy x-ray absorptiometry-based diagnosis of osteopenia rather than osteoporosis, and most of those on alendronate were on double the dose that is Food and Drug Administration (FDA)-approved for prevention of osteoporosis. Some alendronate users in our survey were switched to another BP at some point, and others used another BP exclusively—risedronate or zoledronic acid. (We recently received documentation from a patient who sustained an AFF after almost 6 yr exclusively on ibandronate.) AFFs in patients using exclusively other BPs may increase in number as these BPs are available for a longer time period, but this is yet to be determined. AFFs appear to be a class effect, although the relative risk of different BPs is undetermined as yet. Most patients were also on BP treatment for longer than the period studied by the manufacturers in the pivotal trials providing the basis upon which the FDA granted approval of the drugs. We hope

that the FDA will strengthen its guidance (10) regarding 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 reported 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 radiological features of AFFs: 70% of that group had prodromal 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 organizations provide an alternative approach to long-term follow-up, but there is no guarantee that all initially treated patients will remain within the system.

Our study reconfirms the acknowledged importance (3, 12, 13) of evaluating long-term BP patients with unexplained 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 continue 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) recommended 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 (usually 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.

Acknowledgments

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Authors' roles included: study design, J.P.S. and C.S.; data collection, J.P.S. and P.S.; data analysis, J.P.S. and C.S.; data interpretation, J.P.S. and W.B.H.; drafting manuscript, J.P.S.; revising manuscript content, J.P.S., W.B.H., C.S., and P.S.; approving final version of manuscript, J.P.S., W.B.H., C.S., and P.S., J.P.S. takes responsibility for the integrity of the data analysis.

Disclosure Summary: Each author states that no financial or material support or consideration has been received in connection with the work on this study and manuscript. J.P.S., C.S., and P.S. state that they have no conflicts of interest to report. W.B.H. has served as a consultant, advisory board member, and speaker for Lilly USA. All the authors have had full access to all raw data, statistical analyses, and material used in the study.

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