Trends in the incidence of atypical femoral fractures and bisphosphonate therapy

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ABSTRACT

Purpose. To report the trends in the incidence of typical and atypical femoral fractures (AFF) in patients aged >50 years from 2009 to 2014 and in the prescription of bisphosphonates for osteoporosis from 2001 to 2013 in Australia.

Methods. 175 patients aged >50 years presenting to our hospital with an AO type 32 femoral shaft fracture between October 2009 and October 2014 were identified using a trauma database. Of them, 21 male and 110 female patients with a mean age of 75 years were reviewed. Radiographs were reviewed by 2 investigators blinded to the use of bisphosphonates. The femoral shaft fractures were classified as typical or atypical using the American Society of Bone and Mineral Research definition, and their annual incidence was compared. The trend and number of prescriptions for various bisphosphonates in Australia was determined using the Pharmaceutical Benefits Scheme statistics from 2001 to 2013.

Results. Of the 131 femoral shaft fractures, 65 were typical and 66 were atypical subtrochanteric (n=19) or diaphyseal (n=47) fractures that were complete (n=60) or incomplete (n=6). Four patients had sequential bilateral AFF. The 66 AFFs accounted for 5% of hip and shaft fractures. Women accounted for 80% of all femoral shaft fractures and 95% of AFF. The proportion of AFF was higher in women than men (63/110 vs. 3/21, relative risk=3.95, 95% CI=1.37-11.39, p=0.0006). The mean length of hospital stay was 9.7 days shorter in the AFF patients (14.1 vs. 23.8 days, 95% CI=2.6–16.8 days, p=0.008). Patients with AFF were 8 years younger than those with proximal femoral fracture (73 vs. 81 years, p<0.0001). There was no trend in the annual incidence or proportion of AFF from 2009 to 2014 (p=0.70). The bisphosphonate usage was highest in 2007 with 260,000 yearly patient treatments and had declined by 30% by the end of 2013.

Conclusion. AFF accounted for half of all femoral shaft fractures in patients aged >50 years. Women accounted for 80% of all femoral shaft fractures and 95% of AFF. The incidence of AFF was no longer increasing possibly related to decreased prescription of bisphosphonates in preceding years.

Key words: diphosphonates; femoral fractures; fractures, stress; incidence
INTRODUCTION

Bisphosphonates have been reported to be effective in decreasing the incidence of proximal femoral and other fragility fractures in osteoporotic patients. Nonetheless, bisphosphonate use is associated with rare occurrence of atypical femoral fractures (AFF). AFFs occur more commonly in women, Asian race people, and people with disadvantageous femoral geometry including varus alignment, smaller canal and larger offset. Epidemiological and hospital-based studies have reported a decrease in the age-adjusted rate of proximal femoral fragility fracture and an increase in AFFs over time.

Newer bisphosphonates are biologically stable pyrophosphate analogues that are incorporated into areas of active bone turnover and remain potent osteoclast inhibitors with a half-life of 5 to 10 years. The risk of AFF increases significantly after 5 years of continuous bisphosphonate use and decreases rapidly after cessation. Long-term (10 years) treatment has not been shown to have additional advantage in fracture prevention compared to stopping therapy after 5 years. Awareness of the prolonged drug efficacy and potential harm of long-term bisphosphonate treatment is important for patients who have been on continuous treatment.

This study aimed to report the trend in annual incidence of typical and atypical femoral fractures in patients aged >50 years from 2009 to 2014 and the trend in prescription of bisphosphonates from 2001 to 2013 in Australia.

MATERIALS AND METHODS

Using a trauma database, 175 patients aged >50 years presenting to our hospital with an AO type 32 femoral shaft fracture between October 2009 and October 2014 were identified. 44 patients with periprosthetic fracture, fracture through metastasis, shaft fracture extending above the lesser trochanter or distal to the supracondylar flare were excluded. The remaining 21 male and 110 female patients with a mean age of 75 years were reviewed. Proximal femoral fractures were 7 times more common than diaphyseal fractures during the study period.

According to the American Society of Bone and Mineral Research, AFF is defined as fracture located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare with at least 4 of the following 5 major criteria: (1) minimal or no trauma such as fall from standing, (2) fracture originates at lateral cortex and is largely transverse or short oblique, (3) complete fractures are associated with a medial spike, whereas incomplete fractures involve only the lateral cortex, (4) minimal or no comminution, and (5) localised periosteal or endosteal thickening in the lateral cortex (‘beaking’). Other minor features (not necessary conditions) include (1) generalised increase in cortical thickness of diaphysis, (2) unilateral or bilateral prodromal symptoms, (3) bilateral incomplete or complete fracture, and (4) delayed fracture healing.

Radiographs were reviewed by 2 independent investigators to classify the femoral shaft fractures into typical or atypical using the American Society of Bone and Mineral Research definition. The interobserver reliability was 98% and the Cohens kappa was 0.95; 3 discrepancies were assessed by the senior investigator. The 2 groups were compared with the t test for continuous variables and the Fisher’s exact test for categorical variables. The trend and number of prescriptions for various bisphosphonates in Australia was determined using the Pharmaceutical Benefits Scheme statistics from 2001 to 2013.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atypical fractures (n=66)</th>
<th>Typical fractures (n=65)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (no. of patients)</td>
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<tr>
<td>Male</td>
<td>3</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>63</td>
<td>47</td>
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<tr>
<td>Location (no. of patients)</td>
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<td>Subtrochanteric</td>
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<tr>
<td>Shaft</td>
<td>47</td>
<td>26</td>
<td></td>
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<tr>
<td>Mechanism (no. of patients)</td>
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<tr>
<td>High energy</td>
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</tr>
<tr>
<td>Low energy</td>
<td>63</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Mean±SD age (years)</td>
<td>73.0±9.92</td>
<td>76.5±12.4</td>
<td>0.0737</td>
</tr>
<tr>
<td>Mean±SD length of hospital stay (days)</td>
<td>14.1±8.7</td>
<td>23.8±28</td>
<td>0.0081</td>
</tr>
</tbody>
</table>
RESULTS

Of the 131 femoral shaft fractures, 65 were typical and 66 were atypical subtrochanteric (n=19) or diaphyseal (n=47) fractures that were complete (n=60) or incomplete (n=6). Four patients had sequential bilateral AFF. The 66 AFFs accounted for 5% of hip and shaft fractures.

Women accounted for 80% of all femoral shaft fractures and 95% of AFF. The proportion of AFF was higher in women than men (63/110 vs. 3/21, relative risk=3.95, 95% CI=1.37-11.39, p=0.0006, Table). The mean length of hospital stay was 9.7 days shorter in the AFF patients (14.1 vs. 23.8 days, 95% CI=2.6–16.8 days, p=0.008, Table). Patients with AFF tended to be younger than those with typical fractures (73.0 vs. 76.5 years, p=0.074, Table). Patients with AFF were 8 years younger than those with proximal femoral fracture (73 vs. 81 years, p<0.0001).

The highest total number and proportion of AFF (21 and 60% respectively) occurred in 2010-2011. Contrary to earlier reports of increasing incidence of AFF following the generalised use of bisphosphonates, there was no trend in the annual incidence or proportion of AFF from 2009 to 2014 (p=0.70, Fig. 1).

There was a dramatic rise in the use of alendronate from 2001 to 2005 and risedronate from 2003 to 2005. Since 2006, the use of alendronate and risedronate has declined steadily, and has coincided with a rise in the newly listed formulations of both drugs combined with vitamin D and calcium. The combined prescription of these drugs was less than the peak prescription of alendronate alone in 2006 (Fig. 2). The bisphosphonate usage was highest in 2007 with 260,000 yearly patient treatments or 3.4

**Figure 1** Annual incidence of typical and atypical femoral fractures (AFF) and proportion of AFF

**Figure 2** Bisphosphonates for osteoporosis patients weighted to years of patient treatment 2001 to 2013

**Figure 3** Combined weighted totals of each bisphosphonate by active drug and total 2001 to 2013. 1 denotes subsidised prescription for alendronate and risedronate, 2 subsidy expanded to patients aged >70 years without a fracture with a t-score of <-3.0, and 3 subsidy requirement reduced to a t-score of <-2.5
DISCUSSION

In our study, 66 (50.4%) of 131 femoral shaft fractures in patients aged >50 years were AFF and accounted for 5% of the total number of hip and shaft fractures. These proportions were higher than those in a UK study at 2 large hospitals from 2008 to 2010 that AFF accounted for 7% of femoral shaft and 0.8% of total hip and shaft fractures, and in an Australian study that AFF accounted for 30% of shaft fractures from 2007 to 2011 and the rate was increasing.

In our study, there was no trend in the annual incidence or proportion of AFF from 2009 to 2014. This is contrary to earlier epidemiological studies that have shown an increasing incidence of AFF by up to 10.4% per year and a decreasing or stable incidence of femoral neck fractures. The earliest reports of minimal trauma stress fracture associated with bisphosphonate use appeared in 2005-2008, a decade after bisphosphonates became available. As the risk of AFF has been shown to increase progressively after 5 years of use, there is a lag of several years in the rate of AFF. Over the same time period, the rate of proximal femoral fractures at our hospital was unchanged with a mean of 240 per year. It is important to repeat this study in 5 years to look for a reduction in AFF rate and an increase in proximal femoral fragility fractures, both associated with the decrease in bisphosphonate prescribing.

The higher incidence of AFF in women is expected. Women are more likely to develop osteoporosis and sustain fragility fractures, and more women qualify for subsidised bisphosphonate therapy. Women are more likely to have disadvantageous anatomic features (such as smaller shaft diameter, larger femoral offset, and increased curvature) that predispose to AFF after bisphosphonate therapy.

Early studies reported a high complication rate in AFF, with delayed healing and consequent high reoperation rate from non-union or hardware failure. This may be due to the prolonged half-life of bisphosphonates and their effect on fracture remodelling. Although bisphosphonates prevent fragility fractures that are relatively easy to treat, they risk causing atypical fractures for which treatment is more challenging. Healing is usually delayed but generally reliable with 98% union rate after a mean of 8.3 months. In our study, the length of hospital stay was 40% shorter in patients with AFF than with typical fractures. This may be because AFF patients were younger and thus at lower surgical risk and may have progressed faster with rehabilitation. Furthermore, 90% of AFF were non-comminuted, simple fractures that allowed reliable postoperative stability. Lastly, there was a higher proportion of high-energy mechanism in typical than atypical fractures.

In Australia, the Pharmaceutical Benefits Scheme started to subsidise prescription costs for alendronate and zoledronic acid in 2009. In 2007, the subsidy was expanded to include patients aged >70 years without a minimal trauma fracture with a bone-mineral density t-score <3.0, and in 2012 expanded further to t-score <2.5. A Medicare rebate for bone-mineral density testing was introduced for patients aged >70 years. As a result of an ageing population and broadened eligibility criteria, the number of people qualifying for and prescribed bisphosphonate therapy had increased and this may be a probable cause for the increase in AFF rate until 2007. The number of prescriptions has decreased since 2007 by a third and this may have contributed to the plateau in yearly incidence of AFF.

The possible reasons for the reduction in bisphosphonate prescription after 2007 include: (1) patients who would benefit from treatment were not receiving it, (2) awareness of potential harm restricted treatment uptake, and (3) awareness of prolonged efficacy after stopping and potential harm of prolonged continuous use resulted in patients ceasing treatment after a given time.

There were several limitations to our study. Limited by digital radiology availability, we only assessed femoral shaft fractures over 5 years from 2009 to 2014. The duration of bisphosphonate use in our patients was not recorded. Patients were not sub-divided by race or femoral geometry; female sex, Asian race, and varus alignment are known risk factors for AFF. Some patients with incomplete fracture may have presented elsewhere. By grouping the weighted number of prescriptions for different bisphosphonates, we assumed that they were all likely to contribute to the risk of AFF in a number of patients because of their similar mode of action on osteoclast inhibition. However, relative risks of AFF vary in different bisphosphonates. Most studies have focused on alendronate; long-term trials with other bisphosphonates are needed. The national prescribing statistics may not accurately reflect regional practice of our population.

CONCLUSION

AFF accounted for half of all femoral shaft fractures in patients aged >50 years. Women accounted for 80% of all femoral shaft fractures and 95% of AFF. The
incidence of AFF was no longer increasing possibly related to decreased prescription of bisphosphonates in preceding years.

REFERENCES


DISCLOSURE

No conflicts of interest were declared by the authors.