Atypical femoral fractures and bisphosphonate treatment

We performed a retrospective review of all patients admitted to two large University Hospitals in the United Kingdom over a 24-month period from January 2008 to January 2010 to identify the incidence of atypical subtrochanteric and femoral shaft fractures and their relationship to bisphosphonate treatment. Of the 3515 patients with a fracture of the proximal femur, 156 fractures were in the subtrochanteric region. There were 251 femoral shaft fractures. The atypical fracture pattern was seen in 27 patients (7%) with 29 femoral shaft or subtrochanteric fractures. A total of 22 patients with 24 atypical fractures were receiving bisphosphonate treatment at the time of fracture. Prodromal pain was present in nine patients (11 fractures); 11 (50%) of the patients on bisphosphonates suffered 12 spontaneous fractures, and healing of these fractures was delayed in a number of patients. This large dual-centre review has established the incidence of atypical femoral fractures at 7% of the study population, 81% of whom had been on bisphosphonate treatment for a mean of 4.6 years (0.04 to 12.1).

This study does not advocate any change in the use of bisphosphonates to prevent fragility fractures but attempts to raise awareness of this possible problem so symptomatic patients will be appropriately investigated. However, more work is required to identify the true extent of this new and possibly increasing problem.

Recent literature has suggested a possible link between the prolonged use of bisphosphonates and atypical fractures in the subtrochanteric and shaft regions of the femur.1-6 These fractures have a transverse or short oblique orientation with a simple fracture and are associated with hypertrophy of the cortex in the shaft (Fig. 1). When the fracture is complete there may be a medial spike. Incomplete fractures involve only the lateral cortex. These fractures occur either spontaneously or as a result of a low-energy injury.

Bisphosphonates reduce the incidence of fragility fractures, and the United Kingdom's National Institute for Health and Clinical Excellence (NICE) has recommended alendronate as the drug of choice in the primary and secondary prevention of fragility fractures in postmenopausal women.7,8 Bisphosphonates act to reduce bone resorption by inducing osteoclast apoptosis.9 They achieve this by binding to the inorganic component of bone, which is then endocytosed (a process by which cells engulf and absorb molecules) by the osteoclast, resulting in inhibition of the mevalonate pathway and inducing cell death. The half-life of bisphosphonates is between five and ten years.10 Several reports have suggested that the decreased rate of bone turnover associated with the reduction in osteoclastic resorption leads to increased bone mineralisation and causes the bone to become brittle.1-4,11,12 The result of these changes, combined with the failure to repair the micro-damage, may lead to a long-term increase in the risk of fracture. Although the association of atypical fractures and bisphosphonates has not been proved, this could be an important public health issue, and the incidence of long-term complications will need to be factored into any evaluation of the socioeconomic benefits of programmes which are designed to prevent fractures.

We have recently observed a number of fractures with this characteristic pattern in the subtrochanteric and shaft regions of the femur, which prompted us to review all subtrochanteric and femoral shaft fractures treated in our institutions between January 2008 and January 2010 in order to identify the frequency of these atypical fractures in patients who receive bisphosphonates.

Patients and Methods

We conducted a retrospective review of all patients admitted to two large university
hospitals over a 2 year period commencing in January 2008. One hospital (Nottingham) covered a population of 750,000 and the other (Belfast) a population of 1,020,000. These hospitals admit approximately 800 and 1,000 patients with hip fractures per year, respectively. All patients with a subtrochanteric or femoral shaft fracture were identified from the prospective trauma databases of the two hospitals.13

The plain radiographs of all patients with either a subtrochanteric or a femoral shaft fracture were independently reviewed by an orthopaedic consultant or specialist registrar (RNT, SHJMcC, JRME, JRAP, CGM) who was unaware of the patient’s history or medication. Fractures with the atypical pattern of a simple transverse fracture line in an area of cortical hypertrophy were identified. For each of these patients, the use of bisphosphonates and their duration, the mechanism of injury and the history of prodromal pain were recorded. A history of corticosteroid use, metabolic bone disease and previous fractures were also ascertained. This information was obtained from the medical records, our fracture database, and the patients’ general practitioners.

Results
During the two years commencing 1 January 2008 a total of 3,515 patients with a fracture of the proximal femur were treated; 156 of these fractures were in the subtrochanteric region, and there were 251 femoral shaft fractures.

The atypical fracture pattern was seen in 29 femurs in 27 patients. Bilateral sequential subtrochanteric fractures occurred in one patient (nine months apart) and bilateral simultaneous shaft fractures occurred in one patient; one other patient sustained sequential bilateral shaft fractures, (two years apart: as only one occurred within the study period, only one has been included).

The atypical fracture pattern was seen in 18 (7%) of 251 femoral shaft fractures and 11 (7%) of 156 subtrochanteric fractures. This represents 0.8% of all hip and shaft fractures, and 7% of both the subtrochanteric and femoral shaft fractures treated in this period. The mean age of the 27 patients at time of fracture was 73.6 years (52 to 91 years) and 23 (85%) were female.

The patient was being treated with bisphosphonates in 16 of 18 atypical femoral shaft fractures and eight of 11 atypical subtrochanteric fractures. Thus, at the time of fracture, 22 of the 27 patients (including both patients with bilateral injuries, therefore 24 of 29 fractures) in the atypical fracture group were receiving bisphosphonate therapy. Alendronate was the bisphosphonate used in 17 patients (including both patients with bilateral injuries, therefore 19 fractures). The mean duration of treatment prior to fracture for the group as a whole was 4.6 years (0.04 to 12.1). A summary of the duration of bisphosphonate therapy is shown in Figure 2.

Of these 24 fractures in patients on bisphosphonates, prodromal pain was reported in eleven fractures (nine patients) and had been present for between six weeks and three years prior to the fracture. Three patients had previous pelvic or femoral radiographs that demonstrated a localised fusiform expansion in an area of cortical thickening in the same location as the eventual fracture.

In total, eight of the 27 patients with the atypical fracture pattern had prior treatment with corticosteroids (six orally and two inhaled). Only one of the patients on steroids was not taking a bisphosphonate.

In all, five patients (three women and two men) had an atypical fracture pattern with the radiological changes associated with bisphosphonate therapy but had never taken bisphosphonates. Of these, one had Paget’s disease, one took steroids for chronic obstructive airways disease and one took methotrexate for psoriasis. Two had no potential risk factors. None had active cancer.

The fracture occurred spontaneously in 13 (45%) of 29 of the atypical fractures, or by a low energy injury (i.e fall from standing height) in 16 (55%) of 29 of the atypical fractures. In the 22 patients (24 fractures) who were taking bisphosphonates, 12 fractures occurred spontaneously and 12 were due to a low-energy injury. In those not taking bisphosphonates one of five fractures occurred spontaneously and four were due to a low-energy injury. These data are presented in Figure 3.

Complete follow-up was achieved in 20 patients. In patients who were taking bisphosphonates (n = 19) the mean time to radiological union was six months (3 to 15), with four patients taking > six months and two taking > one year (Fig. 4). The longest time to union (18 months) occurred in a patient who was not taking bisphosphonates. Each of these
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Of those fractures with delayed union, one was dynamised, the others were managed expectantly.

Case report. An 88-year-old woman presented to her general practitioner in December 2006 with pain in the left hip. Plain radiographs were normal and no further investigations were undertaken. In February 2009, aged 91, she was admitted with a low-energy subtrochanteric fracture sustained when she tripped over. She had been on alendronate for three years and had an unusual fracture pattern. The radiograph taken in December 2006 was reviewed and a small localised area of fusiform cortical hypertrophy was seen in the subtrochanteric region. This area corresponded to the site of the subsequent fracture (Figs 1 and 5).

The fracture was stabilised with an antegrade nail. There were no post-operative complications and the immediate post-operative radiograph clearly demonstrates the fracture pattern (Fig. 5b).

At two months post-operatively it was noted that callus formation was slow. In November 2009 fracture union had still not occurred and the distal locking screws were removed and the fracture subsequently united (Figs 5c and 5d).

fractures had been managed with antegrade cephalomedullary nailing. Of those fractures with delayed union, one was dynamised, the others were managed expectantly.
Discussion

Bisphosphonates reduce the risk of fracture in osteoporotic patients. Clinical trials have confirmed their efficacy, and compared with placebo controls bisphosphonates have shown significant reductions in the relative risk of new vertebral and peripheral fractures (including the hip) of up to 51\%. The Fracture Intervention Trial (FIT) demonstrated the ability of bisphosphonates to increase bone mineral density, particularly in the neck of the femur, hip and spine. Their use is actively encouraged through clinical guidelines drawn up by the NICE and the Scottish Intercollegiate Guidelines Network.

However, recent literature has raised the possibility of a link between bisphosphonate use and the occurrence of low-energy or spontaneous subtrochanteric and femoral shaft fractures with a characteristic pattern in an area of cortical hypertrophy. Our study has confirmed these findings but interestingly, whereas most of the current literature has concentrated primarily on atypical subtrochanteric fractures, our series shows that similar numbers occur in the femoral shaft.

The precise aetiology of these fractures remains uncertain. Bone biopsies in patients on long-term alendronate treatment reveal severe suppression of bone turnover and a diminished bone matrix and decreases in biochemical markers of bone turnover have also been demonstrated. Remodelling removes micro-cracks and replaces them with new bone in response to the stresses of daily life. It is hypothesised that bisphosphonates suppress bone remodelling, leading to the accumulation of micro-damage and the development of highly mineralised but brittle bone. As micro-cracks propagate, the bone becomes more susceptible to micro-damage, especially under physiological loads, thereby accumulating further micro-cracks and, in time, stress reactions which can develop into complete fractures.

Bisphosphonates may also cause impaired fracture healing, leading to the suggestion that treatment be discontinued during the healing phase. We noted delayed time to radiological union in some, but not all, of our patients. However, this could possibly be due to the fracture being fixed in a degree of distraction.

The question arises whether these atypical fractures are wholly attributable to treatment with bisphosphonates. The answer is probably no, as fractures were found in a number of patients who had never taken bisphosphonates, but our observational study lacked the power to investigate a cause and effect relationship between bisphosphonates and these atypical fractures. The number of patients taking bisphosphonates in our population is unknown, but even if prescription rates could be established, patient compliance...
is a variable that would be impossible to establish. Over a two-year period 7% of subtrochanteric and femoral shaft fractures at our institutions had this abnormal pattern, and 22 of 27 of these patients had been taking bisphosphonates.

A similar radiological type of subtrochanteric fracture has been recognised in adult hypophosphatasia, a rare metabolic bone disease that suppresses bone turnover.20 The question also arises whether these fractures can be anticipated. The presence of prodromal pain is consistent with patients developing micro-cracks, because of suppressed micro-damage repair.1 It was present in nine (41%) of our patients (11 fractures) receiving bisphosphonate treatment with pain from six weeks to three years. Goh et al5 and Kwek et al3 reported rates of prodromal pain of 56% and 76% respectively in their series.

It is recommended that patients receiving alendronate treatment should be screened for prodromal symptoms.3 If there is pain in the hip or thigh, plain radiographs should be taken. If these are normal and pain persists, an MRI scan should be performed.11 In such patients, stopping alendronate should be considered.21

Das De et al19 highlighted a significant incidence of bilateral fractures in patients receiving alendronate and recommended careful surveillance of patients with prior alendronate-related atypical fractures, particularly if they present with pain in the contralateral limb. Three patients in our study sustained bilateral femoral fractures, one simultaneously (Fig. 6) and two occurred sequentially, which emphasises the importance of close surveillance of the contralateral limb, especially in the presence of pain.

Schilcher and Aspenberg22 questioned whether the risks of bisphosphonate-associated fractures are so great that their use in treatment of osteoporosis should be stopped. They calculated that treating their total population (900 000) with bisphosphonates would result in 900 stress fractures, but would prevent 13 500 osteoporotic fractures and hence that treatment was justified. However, to allow an accurate risk–benefit analysis to be performed the true incidence and prevalence of these fractures needs to be established.

Analysis of human iliac crest biopsies has suggested that micro-damage accumulates after a mean of five years of alendronate treatment.12 The United States National Osteoporosis Foundation has recommended a five-year ‘drug-free holiday’ after alendronate treatment of 5 mg/day for five years, stating that this does not lead to an increase in fracture risk and that it could be advantageous.23 The FLEX Trial23 (a long-term extension of the FIT trial) compared the risk of fracture in patients in the five years following discontinuation of alendronate after five years of treatment with those who remained on treatment for ten years. In the first group osteoclast suppression continued

Fig. 6

Images of a 74-year-old female, showing a) femoral abnormalities in a bone scan (left), and b and c) radiographs eight months later showing simultaneous bilateral atypical shaft fractures (centre and right).
for at least a further five years, with no increase in the risk of suffering a vertebral or non-vertebral fracture compared with the second group, and continued suppression of biochemical markers of bone resorption and formation was noted. This is not surprising, as alendronate incorporates itself into the bone matrix and has a half-life of more than ten years.\textsuperscript{24}

A task force appointed by the American Society for Bone and Mineral Research has studied the available evidence\textsuperscript{11} and acknowledges that although there is the biological potential for an association between atypical fractures and bisphosphonates, a clear relationship has yet to be established. The establishment of an international registry was recommended to determine risk factors and optimal management. This might enable the identification of the sub-group of patients who are at risk of developing an atypical fracture so that alternative treatment can be considered.

All hospitals in England, Wales and Northern Ireland now contribute to the National Hip Fracture Database (NHFD). This might allow surveillance of these fractures and accumulate evidence from around 80 000 patients per year but this database does not include femoral shaft fractures, which our survey suggests might be just as commonly involved.

Given our findings of atypical fracture patterns in the femoral shaft and subtrochanteric region which may be associated with long-term bisphosphonate use, there needs to be an awareness of this potential problem in a patient who presents with new onset of thigh or hip pain without a history of trauma and who is receiving long-term bisphosphonates. These patients warrant early investigations. If a patient on bisphosphonates sustains an atypical fracture of the contralateral limb should also be undertaken to look for evidence of contralateral cortical thickening, localised stress reactions or incomplete fractures.

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References


