Bisphosphonate-related bilateral atypical femoral fractures – be aware and beware

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Abstract

Although bisphosphonates have a well established therapeutic role in the prevention of osteoporosis-related fractures, several reports published over the past 5-6 years suggest a possible causative relationship between long-term use of bisphosphonates and development of 'atypical' subtrochanteric and femoral diaphyseal fractures. A high level of clinical suspicion and prompt imaging when these patients present with groin/thigh pain should lead to a timely diagnosis. Appropriate elective management to mitigate against the increased risks of these fractures becoming complete could then be instituted. We present a case of complete bilateral atypical subtrochanteric fractures in a patient on long-term bisphosphonates for osteoporosis. Our objective is to highlight the fracture risk of this patient population; present the current knowledge; and discuss the dilemmas in management of both femora.

Keywords

Osteoporosis, bisphosphonates, bilateral, atypical, femoral fractures

Introduction

Bisphosphonates have a well established therapeutic role in the prevention of osteoporosis-related fractures. They have been shown to reduce the risk of insufficiency fractures of the hip and spine in post-menopausal, osteoporotic females.1,3,4

Over recent years, reports have suggested a direct relationship between long-term use of bisphosphonates and the development of subtrochanteric and femoral diaphyseal fractures with an ‘atypical’ site and configuration. The exact mechanism underlying this apparent increase in fracture risk is still unclear.

We present a case of bilateral atypical complete subtrochanteric fractures in a patient on long-term bisphosphonates for osteoporosis.

Case report

A 60 year old lady was initially diagnosed with osteoporosis in 2005. She had no significant past medical history and apart from hormone replacement therapy (HRT) was not on glucocorticoid treatment or any other prescribed medication. She was a non-smoker and drank very little alcohol. Her bone mineral content at the time was just below the fracture threshold and since she had just stopped her HRT she was offered prophylactic bisphosphonate treatment. She initially opted to postpone therapy but suffered a stress fracture of her third metatarsal in 2006 and was started on oral risedronate 35mg weekly. A follow up bone density scan in 2007 showed an improvement in bone density of both the femoral neck and lumbar spine (T-score -1.8 (femur) and -2.1 (L2)). Bisphosphonate treatment was changed to alendronate in 2008 and she carried on taking this regularly.

In February 2010 she visited her general practitioner complaining of a 3 month history of left hip pain and stiffness and was referred for a plain radiograph of her pelvis (Fig.1). This showed mild focal thickening of the proximal subtrochanteric lateral cortices bilaterally particularly on the left. These findings were not appreciated at the time. A few months later, in May 2010, the patient tripped down two steps and sustained an atypical subtrochanteric fracture of her left femur (Fig. 2) which was treated with a proximal femoral nail antirotation (PFNA) procedure. Early post-operative imaging (Fig. 3) clearly shows that the fracture had occurred through the area of previously demonstrated cortical beaking.
A follow-up pelvic radiograph in September 2010, 4 months following injury, showed two interesting findings (Fig. 4). Apart from showing that fracture healing was progressing satisfactorily, it also showed that the previously noted right lateral cortical beaking had increased in size since injury. A fracture through the left lateral cortex a few centimetres distal to the first fracture was also noted (arrowhead).

Just three weeks later, in October whilst out shopping, she turned awkwardly and suffered yet another atypical complete subtrochanteric fracture of the right femur (Fig. 5) which was again managed with a PFNA procedure (Fig. 6). The right fracture was again noted to run through the site of previously seen cortical thickening. In hindsight, the patient did recall that whilst recovering from her left hip operation and using crutches, she was aware of some pain in her right hip which she had dismissed.

Subsequent investigations including serum parathyroid hormone (PTH), serum vitamin D, skeletal survey, chest x-ray, breast screening and a myeloma screen were all normal. She initially continued on alendronate until she read an article in the local newspaper about atypical femoral fractures, following which she stopped alendronate treatment and continued vitamin D and calcium supplements. The patient was then transferred to our hospital’s Metabolic Disorders Department.

**Discussion**

The lifetime risk of developing an osteoporotic fracture is approximately 50% in females and 25% in males.\(^2\) Subtrochanteric and diaphyseal fractures of the femur account for 7-10% of all hip and femoral shaft fractures.\(^2,3\) Having excluded high-impact trauma and periprosthetic fractures, the ‘atypical’ type accounts for just 1.1–1.7% of all femoral fractures. These fractures have been labelled ‘atypical’ due to their uncommon site and configuration (Table 1), and have been attributed to bisphosphonates use. Atypical fractures appear to be commoner in patients who have been on bisphosphonate therapy, more so in patients who have been treated for over 3 years (median 7 years). They have, however, also been described in patients who have not been exposed to bisphosphonates and the definitive causal relationship is yet to be proven.\(^4,5\)

Bisphosphonates are thought to influence bone metabolism in many ways. The organic matrix of bone is the prime
Contribution to strength and bisphosphonates have been shown to have both positive and negative effects on matrix by affecting the maturation process of collagen. Bisphosphonates are known to reduce bone turnover through their effect on osteoclasts and secondarily osteoblasts, which in turn causes an increase in overall bone mineralisation resulting in increased bone strength. Paradoxically, however, reduction of bone turnover also results in accumulation of advanced glycation end products (AGEs) which in turn are associated with rendering bone increasingly brittle. Bisphosphonates also play a role in suppressing excessive bone remodelling which would increase bone fragility. Bone remodelling is also responsible, however, for the removal of microdamage that accumulates with use, and its suppression by bisphosphonates can lead to accumulation of tiny cracks which could weaken the bone structure. It is currently thought that a combination of these factors may be involved in the development of atypical femoral fractures. The clinical importance of the side-effects of bisphosphonates on human bone is not entirely clear. The existing published reports of these atypical fractures in patients exposed to bisphosphonates have merely highlighted a potential link between the two and more scientific research is required to confirm this.2,3,4,6

Shane et al. have defined a list of major and minor features for the diagnosis of complete and incomplete atypical fractures of the femur in an attempt to ensure that future studies report on the exact same condition (Table 1). Theyclaim that all major features must be present to qualify a fracture as ‘atypical’, as opposed to the more common types of hip and femoral shaft fractures. Minor features may or may not be present.3 Most of the described features, including the location, absence of significant trauma, fracture configuration, prodromal pain, bilaterality, lateral cortical thickening and generalised diaphyseal cortical thickening had been previously documented as typical of these fractures.1,2,4,5. Prodromal pain has been reported in 70-75% of cases2,3 and bilateral fractures are seen in 28%.2 Femoral neck fractures, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures and pathological fractures associated with primary or secondary bone tumours have been specifically excluded.3 These fractures should be differentiated from Looser zones and sports-related stress fractures both of which typically involve the medial cortex.2,3

A recent prospective Study of Osteoporotic Fractures (SOF) has shown that the incidence of subtrochanteric fractures is very low (3/10000 person-years) compared to an overall incidence of hip fractures of 103/10000 person-years.7 Screening of all patients on long-term bisphosphonates in search of early features of atypical fractures is not, therefore, cost-effective and is not thought to be warranted.1 It is however advised that any patient, who is known to be on long-term bisphosphonates therapy, and presents with groin/hip pain should be imaged.2,5 Conventional plain film imaging is the first line of investigation. Anteroposterior and lateral projections of the proximal femora down to the distal femoral metaphyses should be obtained. Typical features of incomplete atypical fractures may initially include a focal thickening of the lateral cortex resulting in what has been described as ‘beaking’ or ‘flaring’. A transverse or mildly oblique fracture line may subsequently appear typically starting at the lateral cortex and progressing medially. When the fracture becomes ‘complete’ it may be associated with a medial cortical spike.3 More advanced imaging modalities should be

| Table 1: Atypical femoral fracture: major and minor featuresb |
|-----------------|-----------------|
| **Major features** | **Minor features** |
| • Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare | • Localised periosteal reaction of lateral cortex (often referred to in the literature as beaking or flaring) |
| • Associated with no or minimal trauma as in a fall from standing height or less | • Generalised increase in cortical thickness of the diaphysis |
| • Transverse or short oblique configuration | • Proximal symptoms such as dull or aching pain in the groin or thigh |
| • Not comminuted | • Bilateral fractures and symptoms |
| • Complete fractures extend through both cortices and may be associated with a medial spike; | • Delayed healing |
| Incomplete fractures involve only the lateral cortex | • Comorbid conditions e.g. vitamin D deficiency, rheumatoid arthritis |
| | • Use of pharmaceutical agents e.g. bisphosphonates, glucocorticoids, proton pump inhibitors |

bSpecifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumours, and periprosthetic fractures.

bAll major features are required to satisfy the case definition of atypical femoral fracture. None of the minor features are required but sometimes have been associated with these fractures.

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**Controlled vocabulary entries**
- Atypical femoral fracture
- Bone turnover
- Bisphosphonates
- Osteoporosis
considered, in patients with a history of prodromal thigh or hip pain, when plain x-rays are normal or inconclusive. An Isotope bone scan may be utilised and, if positive, will show an intense focus of uptake at the fracture site with a more subtle uptake zone surrounding it. The advantages of radionuclide imaging are the ability to evaluate both thighs, early diagnosis of bilateral fractures and demonstration of otherwise occult fractures.

Magnetic Resonance Imaging (MRI) can similarly detect the focal cortical thickening which is typically of low signal on both T1- and T2-weighted sequences, as well as the surrounding marrow oedema which is of diffuse intermediate/low signal on T1-weighted sequences and of intermediate/high signal on fluid sensitive sequences such as STIR and T2-weighted fat suppressed sequences. The fracture-line arising in the lateral cortex may also be visible on certain occasions. Multi-Detector Computerised Tomography (MDCT) can also be used to evaluate the bony architecture in more detail and may demonstrate the focal lateral cortical thickening and the lucent fracture line arising laterally.³

Subtrochanteric complete fractures have a significant effect on patients’ morbidity and mortality. Two years post-injury, up to 50% of patients had still not returned to their premorbid state of social well-being. A mortality rate of 14% at 12 months and 25% at 24 months has been reported.³ Bisphosphonates could also be responsible for delayed fracture healing with delayed or absent healing being reported in 39% of cases.¹³ Bisphosphonates are known to heal by endochondral ossification of cartilage callus. Although bisphosphonates do not interfere with this aspect of the healing process, their negative effect on bone remodelling delays fracture consolidation and development of mature bone. Incomplete fractures, on the other hand, heal by bone remodelling and their healing is therefore delayed by bisphosphonates treatment. Bisphosphonates are also thought to have an inhibitory effect on angiogenesis which in turn may have a negative effect on fracture healing.³ It is therefore crucial to aim at preventing these fractures from happening, where possible, and manage them effectively both medically and surgically.

Similar to treatment of any other disease, the decision to start patients on bisphosphonates therapy for their osteoporosis should be taken based on the known advantages and potential risks. It is not possible to have one management protocol in place to cover all clinical scenarios, and clinical expertise and judgement should be used. FRAX, the WHO population-specific Fracture Risk Assessment Tool (www.sheffield.ac.uk/FRAX/) could be used to evaluate risk.¹

The current general opinion regarding medical treatment is as follows:

- Patients with a low risk of developing osteoporosis-related insufficiency fractures should not be started on bisphosphonates. In the United States, guidelines suggest treating any patient with a 10 year major osteoporotic risk of >20% or a hip fracture risk of >3%.³

- Those with spinal osteoporosis but normal or near normal hip bone mineral density (BMD) should be considered for alternative treatments.³

- Bisphosphonate treatment is known to be effective in reducing risk of insufficiency fractures for at least 5 years. Continuation of therapy beyond this time may be necessary based on estimated fracture risk. It is however uncertain if risk reduction will continue beyond the first 5 years and continuation of therapy beyond this point warrants an annual reassessment.²,⁵,⁹,¹⁰,¹¹

- Suspending treatment for 1 year or more should be considered in patients with a low fracture risk, with no history of insufficiency fractures and a T-score of more than -2.0 to -2.5.²,⁵,⁹,¹⁰,¹¹ There is no generalised agreement as to whether this is of proven benefit. Currently, there are also no guidelines in place indicating if and when bisphosphonates should be restarted following a ‘drug holiday’, but due consideration to restarting should be given if fracture risk increases.

- There is however a strong favoured opinion that bisphosphonates should be discontinued in patients with incomplete or complete atypical fractures and that adequate calcium and vitamin D supplementation should be considered.

- Although the use of teripartide (recombinant parathyroid hormone) in these patients has been claimed to aid fracture healing by increasing bone turnover, no solid clinical evidence exists to substantiate this. It should however be considered in situations of fracture non-union.¹²,³

There is, as yet, no agreed surgical management protocol for these fractures. It is however agreed that where orthopaedic intervention is required full-length intramedullary nail reconstruction is the method of choice as it allows endochondral fracture repair which is not inhibited by bisphosphonates.³,⁴ Locking plates are, on the other hand not recommended as they do not allow endochondral healing and have a high risk of non-union.³,⁴ The general opinion is as follows:

- Complete atypical fractures need to be stabilised by intramedullary nailing.

- Prophylactic intramedullary nailing is advised for patients with incomplete fractures in the presence of prodromal pain.¹,³

- In the absence of pain, a 2 to 3 month period of conservative partial-weight-bearing should be attempted, with prophylactic nailing considered if patients become symptomatic. If conservative treatment is successful, reduced activity should be enforced until no residual oedema is seen on MRI.¹,³

The risk of a second complete fracture of the contralateral femur is high as shown in our case. The management of the contralateral femur following an initial atypical fracture has not been analysed in depth. There are four potential
management plans. The contralateral hip should be imaged by plain radiography in the first instance. The options for prophylactic intramedullary nailing of the contralateral femur are then as follows:

• Operate ONLY when patient is symptomatic AND either plain radiography or isotope bone scan is abnormal.
• Operate when patient is symptomatic even if imaging is normal.
• Operate when imaging is abnormal even if patient is asymptomatic.
• Prophylactically nail the contralateral femur at the same surgical sitting as the initial emergency nailing independent of symptoms or imaging findings.

As clearly seen in our case, the contralateral femoral changes progressed very rapidly following the initial injury. The reason for this rapid change is thought to be the markedly increased mechanical strain placed onto the uninjured lower limb during the postoperative recovery. It must be remembered that the effects of bisphosphonates on bone are systemic and that the contralateral femur must also be thought of as inherently weak. The widely accepted orthopaedic surgical protocol used in the management of unilateral slipped upper femoral epiphysis (SUFE), which is known to occur bilaterally in a third of patients, should be borne in mind when formulating a management protocol for patients presenting with their first episode of atypical fractures. In view of the 28% risk of bilateral fractures and the increased morbidity and mortality associated with these fractures, it is our belief that following detailed discussion informing patients of the advantages and risks carried by the available options, prophylactic nailing of the contralateral femur at the same time as emergency nailing of the presenting fractured femur is probably the most advantageous.

Conclusion

Bisphosphonates have been shown to reduce the risk of insufficiency fractures of the hip and spine in post-menopausal, osteoporotic females. Several reports suggest a relationship between long-term use of bisphosphonates and the development of fractures, and the definitive causal relationship is, however, yet to be proven and more research projects are urgently needed. Early diagnosis and appropriate management of these fractures, as well as exclusion of bilateral disease, is of paramount importance since it may reduce the morbidity and mortality risk associated with 'complete' fractures.

References