MINIREVIEWS

Current concepts in the management of bisphosphonate associated atypical femoral fractures

Branavan Rudran, Jonathan Super, Rajan Jandoo, Victor Babu, Soosai Nathan, Edward Ibrahim, Anatole Vilhelm Wiik

ORCID number: Branavan Rudran 0000-0002-2323-1763; Jonathan Super 0000-0003-2082-2813; Rajan Jandoo 0000-0002-1643-7835; Victor Babu 0000-0001-6238-9072; Soosai Nathan 0000-0002-9457-7382; Edward Ibrahim 0000-0001-5476-6552; Anatole Vilhelm Wiik 0000-0003-0937-7675.

Author contributions: All authors were involved in the write up of this review.

Conflict-of-interest statement: There are no conflicts of interest from the contributing authors.

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Manuscript source: Invited manuscript

Branavan Rudran, Rajan Jandoo, Victor Babu, Soosai Nathan, Edward Ibrahim, Anatole Vilhelm Wiik, Department of Orthopaedic Surgery, Chelsea and Westminster NHS Trust, London TW7 6AF, United Kingdom

Branavan Rudran, Jonathan Super, The MSk Lab, Imperial College London, London W12 0BZ, United Kingdom

Anatole Vilhelm Wiik, Department of Surgery and Cancer, Charing Cross Hospital, London W6 8RF, United Kingdom

Corresponding author: Anatole Vilhelm Wiik, BSc, MBBS, MD, Doctor, Lecturer, Department of Surgery and Cancer, Charing Cross Hospital, Fulham Palace Road, 7th Floor East Wing, London W6 8RF, United Kingdom. a.wiik@imperial.ac.uk

Abstract

Bisphosphonates are a class of drugs used as the mainstay of treatment for osteoporosis. Bisphosphonates function by binding to hydroxyapatite, and subsequently targeting osteoclasts by altering their ability to resorb and remodel bone. Whilst aiming to reduce the risk of fragility fractures, bisphosphonates have been associated with atypical insufficiency fractures, specifically in the femur. Atypical femoral fractures occur distal to the lesser trochanter, until the supracondylar flare. There are a number of the differing clinical and radiological features between atypical femoral fractures and osteoporotic femoral fractures, indicating that there is a distinct difference in the respective underlying pathophysiology. At the point of presentation of an atypical femoral fracture, bisphosphonate should be discontinued. This is due to the proposed inhibition of osteoclasts and apoptosis, resulting in impaired callus healing. Conservative management consists primarily of cessation of bisphosphonate therapy and partial weightbearing activity. Nutritional deficiencies should be investigated and appro-priately corrected, most notably dietary calcium and vitamin D. Currently there is no established treatment guidelines for either complete or incomplete fractures. There is agreement in the literature that nonoperative management of bisphosphonate-associated femoral fractures conveys poor outcomes. Currently, the favoured methods of surgical fixation are cephalomedullary nailing and plate fixation. Newer techniques advocate the use of both modalities as it gives the plate advantage of best reducing the fracture and compressing the lateral cortex, with the support of the intramedullary nail to stabilise an atypical fracture with
increased ability to load-share, and a reduced bending moment across the fracture site. The evidence suggests that cephalomedullary nailing of the fracture has lower revision rates. However, it is important to appreciate that the anatomical location and patient factors may not always allow for this. Although causation between bisphosphonates and atypical fractures is yet to be demonstrated, there is a growing evidence base to suggest a higher incidence to atypical femoral fractures in patients who take bisphosphonates. As we encounter a growing co-morbid elderly population, the prevalence of this fracture-type will likely increase. Therefore, it is imperative clinicians continue to be attentive of atypical femoral fractures and treat them effectively.

Key Words: Bisphosphonates; Atypical fracture; Surgical fixation; Atypical femoral fracture; Osteoporosis

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INTRODUCTION

Bisphosphonates are a class of drugs used as the mainstay of treatment for osteoporosis, as well as other metabolic bone diseases worldwide. Osteoporosis is a systemic disease resulting primarily in a low bone mineral density. It is defined by the World Health Organisation as a T score < -2.5 SD below the mean[1]. It is characterised by a deterioration in bone micro-architecture, and subsequent increased susceptibility to fracture[2]. This results in a significant health, social and economic burden to society [3].

Whilst aiming to reduce the risk of fragility fractures, bisphosphonates have been associated with atypical insufficiency fractures, specifically in the femur. These atypical fractures account for 1.1% of all femoral fractures[4]. This paper aims to review the mechanism of action of these drugs, their risks, benefits and in particular how associated fractures should be managed. It should aid clinicians in their understanding of this counterintuitive sequela of bisphosphonate use and ensure patients are counselled appropriately when considering commencement of bisphosphonate treatment.

BISPHOSPHONATES

Bisphosphonates function by binding to the inorganic components of bone, namely hydroxyapatite, and subsequently targeting osteoclasts by altering their ability to resorb and remodel bone. All drugs in this class have a chemical structure consisting of two phosphonic acids attached to a carbon atom with two side chains (R1 and R2), which are short and long respectively[5,6]. The chemical structure of the side chains influences the properties of the drug with the short side primarily influencing the...
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Pharmacokinetics while the long influencing the mode of action and potency. Bisphosphonates with higher binding affinity spread through bone slower than their lower affinity counterparts, however, if treatment is stopped, they remain in the bone for longer. The drug is absorbed in its active form with no systemic metabolism required. 50% of the absorbed drug binds to bone surfaces, most avidly at sites of remodelling, whilst the rest is rapidly excreted by the kidneys.

First generation or more commonly “non-nitrogen-containing bisphosphonates” such as etidronate had a very close structural similarity to inorganic pyrophosphate and were incorporated into newly formed adenosine triphosphate (ATP) molecules and absorbed by the osteoclasts. These toxic ATP molecules accumulated inside the cell and resulted in apoptosis. Second and 3rd generation or more commonly “nitrogenous” bisphosphonates such as alendronate, risedronate, ibandronate, pamidronate and zoledronic acid, have nitrogen containing R2 side chains which when absorbed by the osteoclast bind to and inhibit the activity of farnesyl pyrophosphate synthase, a key regulatory enzyme in the mevalonic acid pathway ultimately resulting in impaired formation of the ruffled border and bone resorption.

Currently the National Institute of Clinical Excellence recommends bisphosphonates for any adult who has been identified as being high risk for osteoporotic fragility fracture as per standard risk assessment tools. This is achieved through the use of the fracture risk assessment tool. It must be noted that consideration of individual circumstances and risks/benefit profiles should be considered within the assessment. This ensures a patient led approach to prevention of osteoporosis. The first line option is oral Alendronic acid, which in a 2008 Cochrane systematic review demonstrated a significant reduction in osteoporotic fractures in post menopausal women. Similarly a significant reduction in osteoporotic vertebral fractures was noted when used in primary prevention.

Recognised side effects of bisphosphonate use include gastrointestinal irritation, musculoskeletal pain, osteonecrosis of the jaw, and more recently recognised, atypical femoral fractures. Oral preparations are now able to be given once weekly making the gastrointestinal (GI) side effects much more tolerable. Unfortunately they are still poorly absorbed, even under ideal condition such as being taken sitting up, after a prolonged fast. IV preparations such as pamidronate and zoledronic acid require even less frequent dosing and do not cause the same GI side effects however are subject to acute phase reactions characterised by flu like symptoms.

ATYPICAL FEMORAL FRACTURES

Atypical femoral fractures are insufficiency fractures that can be related to bisphosphonate use and are identified by major and minor criteria (Table 1). Atypical femoral fractures occur distal to the lesser trochanter, until the supracondylar flare. In general, subtrochanteric and diaphyseal femoral fractures account for 5%-10% of all hip and femoral fractures. A small subset of these fractures (17-29%) are classified as atypical. Currently, evidence of association between atypical femoral fractures and bisphosphonate use is based upon observational studies. There is growing concern that the long-term effects of bisphosphonates on bone remodelling could cause a shift in the classical pattern of hip and femoral fractures towards this atypical configuration. A Swedish study based upon their national registry (1521131 women over 55 years old with a 5% bisphosphonate use) found 46 atypical fractures in the 83311 bisphosphonate users over the 3 year period examined, and estimated a crude incidence of 5.5 atypical fractures per 10000 patient years. This compared to 13 atypical fractures seen in the 1437820 non-bisphosphonate users in the same 3-year period. This equates to an estimated incidence of 0.09. Although this study demonstrated a high prevalence of bisphosphonate use in patients with atypical fractures, the absolute risk of this was very small. The authors concluded that with an appropriate indication, the benefits of fracture prevention with bisphosphonate use greatly outweigh the risk of atypical femoral fracture. A similar conclusion was drawn from a study reviewing 10 years of data, indicating risk of atypical femoral fracture increased with longer duration of bisphosphonate use, but that the absolute risk remained low compared with the reduction in risk of other osteoporotic fractures.
Table 1 Atypical femoral fractures are insufficiency fractures that can be related to bisphosphonate use and are identified by major and minor criteria

| Major criteria (all must be met)                                      | Minor criteria (none required)                              |
|---------------------------------------------------------------------|------------------------------------------------------------|
| Fracture line located anywhere between the distal border of the lesser trochanter of the femur to the proximal edge of the supracondylar flare | Localised periosteal reaction at lateral cortex – beaking, flaring |
| Lateral cortex must be involved (incomplete or complete – normally with medial cortical spike) | Generalised, diaphyseal cortical thickening                   |
| Transverse or short oblique fracture line No comminution            | Prodromal groin/thigh pain                                 |
| No or minimal precipitating trauma                                  | Bilateral fracture and symptoms                             |
|                                                                      | Delayed healing                                             |
|                                                                      | Co-morbidities (rheumatoid arthritis, vitamin and mineral deficiencies) |
|                                                                      | Concomitant use of pharmacological agents (BP, corticosteroids, proton pump inhibitors) |
| Exclusions                                                          |                                                            |
| Neck of femur fractures, fractures relating to primary or secondary bone tumours and peri-prosthetic fractures[11]. |                                                            |

**RISK FACTORS OF ATYPICAL FEMORAL FRACTURES**

Despite the common use of bisphosphonates for the treatment of osteoporosis, atypical femoral fractures remain rare. The majority of patients who are treated with bisphosphonates will not sustain a clinical change in their femur. However, the consequence of an atypical femoral fracture can have significant impact of mortality and morbidity. Therefore, it is imperative that risk factors are identified and screened accordingly.

A number of the clinical and radiological features of atypical femoral fractures and osteoporotic femoral fractures are different, indicating that there is a distinct difference in the respective underlying pathophysiology. These features are similar to those found in stress fractures, with radiological evidence of a transverse fracture, lack of comminution, and localised cortical thickening at the fracture site (Figure 1)[11,16]. Clinically, patients may experience prodromal pain, as well as bilateral pathology[17].

### Biological and biochemical

Bisphosphonate therapy has been shown in randomised controlled trials to increase bone density and reduce the risk of fracture in patients diagnosed with osteoporosis [18,19]. However, there is an association with atypical femoral fractures. Although causation between bisphosphonates and atypical femoral fractures is yet to be demonstrated, several properties of bisphosphonates and their effect on bone physiology are considered to play a role in the development of these fractures[11]. The first is the profound effect that bisphosphonates have on bone turnover[20]. This is achieved through suppression of osteoclast activity[21]. Histologically, this results in reduced resorption depth and a decreased activation frequency of new remodelling units[22], the consequence of which is a reduction in the rate of bone formation. This in turn impairs the ability to repair accumulated microdamage that occurs secondary to usual physiological stresses, leading to a two to seven-fold increase after management with bisphosphonates[23,24]. As well as microdamage accumulation, long-term over suppression of bone turnover results in secondary mineralisation of bone[25]. This hyper-mineralised bone may be more susceptible to fracture due to its brittle properties[26]. This remodelling and hyper-mineralisation results in a 20% decrease in bone toughness without a simultaneous reduction in bone mass[27]. The net effect could be explained by an increase in the young’s modulus of the bone, with reduced ultimate tensile strength resulting in a smaller area under the stress-strain curve.

### Genetics

While the aforementioned properties and resultant effects of bisphosphonates on normal physiology are associated with atypical femoral fractures, it remains unclear as to why these effects are not universal. More recently, genetic mutations have been found to influence susceptibility to atypical femoral fractures following bisphosphate therapy, most notably GGPS1[28]. Other variants have been identified to predispose individuals to atypical fractures, irrespective of pharmacological therapy.
A study has highlighted four uncommon polymorphisms associated with atypical femoral fractures, but no common genetic mutations[30]. The presence of a genetic metabolic bone disorder may be another important risk factor in the development of atypical femoral fractures.

Figure 1 Plain radiographs before and after atypical bisphosphonate associated femoral fracture fixation. A: Before atypical bisphosphonate associated femoral fracture fixation; B: After atypical bisphosphonate associated femoral fracture fixation.

Due to the increase in prevalence of bisphosphonate therapy and incidence of atypical femoral fractures, further research will determine the role of molecular genetics in relation to atypical fractures.

**Biomechanical**

Extrinsic bone strength depends on a combination of structural and material properties of the bone itself. The previously mentioned pathological fracture site is the lateral cortex of the femur; the location of maximal tensile stress[31]. The biomechanical alignment of the hip and femur determines the stresses placed upon the lateral cortex[32]. It has been shown that the lateral femoral bowing angle is the main determinant for location of atypical femoral fracture, with a higher lateral femoral bowing angle predisposing to diaphyseal fracture[31]. For this reason, an argument has been made that individuals of Asian descent are at a higher risk of atypical femoral fracture due to a greater natural bowing to the femoral shaft[33]. There is conflicting evidence regarding the effect of bisphosphonates on the extrinsic bone strength[34], warranting further investigation in this field.

**SCREENING**

A transverse line on plain radiographs has become pathognomonic of atypical femoral fractures[35]. Whilst this makes a diagnosis of a complete fracture more obvious, it is essential that incomplete or impending fractures are not missed. When patients present with the aforementioned clinical features of an atypical femoral fracture, in particular those who are recipients of bisphosphonate therapy, a high index of suspicion and close attention to detail with regards to any imaging should be maintained. Close examination for fracture lines in the lateral cortex and localised periosteal thickening is warranted, as the sensitivity and specificity of these signs has been shown to be high[36].

More recently, the role of computed tomography (CT) in the diagnosis and evaluation of atypical femoral fractures has been inspected. It has been shown that patients with atypical femoral fractures have had pre-fracture imaging showing a thicker lateral cortex at the site of the injury compared with that of bisphosphonate users who did not go on to develop a fracture[37]. Another study revealed that 34% of asymptomatic individuals with atypical femoral fractures displayed evidence of radiologic progression, with a mean time to progression of 25.6 mo[38]. Therefore, in the detection of future atypical femoral fractures, computed tomography and magnetic resonance imaging may provide valuable diagnostic information regarding the water and mineral content of bone[39-42]. Dual-energy X-ray absorptiometry (DEXA) combined with further image analysis techniques may further permit the discovery of abnormalities associated with atypical femoral fractures, providing a window of
opportunity for early intervention[41]. Bone scintigraphy provides clinicians with another imaging adjunct to ensure early detection[43]. At present, there are no high quality studies which consider bone scintigraphy compared to magnetic resonance imaging (MRI) for identification of occult fractures in bisphosphonate related atypical femoral fractures. However, a recent meta-analysis on the use of advanced imaging in occult hip fractures of the elderly suggests that CT and bone scan (sensitivity, 79% and 87% respectively) are less sensitive for occult hip fractures compared with MRI[44].

Serum markers provide a clinical value for initiation and monitoring bisphosphonate use. The present definition for osteoporosis is based on the value of bone mineral density (BMD) measured by DEXA or occurrence of fragility fracture. BMD response to bisphosphonate use is slow, which makes monitoring bone turnover difficult. Bone turnover markers (BTM) provide a more real time reflection of bone formation and bone resorption through the monitoring of serum and urine. A comprehensive review by Vasikaran et al[45] demonstrated that high level of BTMs may predict fracture risk independently to BMD for post-menopausal women. Despite the ability of BTM to monitor the pharmacologic effects of osteoporosis, the inconsistency in metrics of measurement and unsuitable trials on the BTM levels with treatment compared to controls limits its use.

MANAGEMENT OF ATYPICAL FEMORAL FRACTURES

Medical management and considerations

At the point of presentation of an atypical femoral fracture, bisphosphonate or any antiresorptive agent should be discontinued. This is due to the proposed inhibition of osteoclasts and apoptosis, resulting in impaired callus healing. Animal studies suggest that there is larger formation of fracture callus, with resultant increase in bone volume and mineral content, but has delayed hard callus remodeling during endochondral fracture repair[46,47]. In contrast, in vivo human studies of human trabecular bone demonstrated bisphosphonates induced osteoclastic proliferation and maturation, with upregulation of type 1 collagen and osteocalcin[48]. It is still unclear whether these medications should be withheld indefinitely or resumed after a certain time period thereby giving the patient a “bisphosphonate holiday”[49,50]. It is important to appreciate that bisphosphonates have different binding and anti-resorptive properties, thus providing a “holiday” from bisphosphonates may have an impact on femoral fractures[51]. Discontinuing bisphosphonates will possibly reverse bone modelling suppression and promote fracture healing. Data from the Kaiser data base suggests that if bisphosphonates are stopped soon after an atypical fracture, then 20% will fracture the contralateral leg, compared to 50% if continued for 3 years after the primary atypical femoral fracture[52]. It must be noted that alternative therapies should be considered if bisphosphonates are discontinued.

Conservative management consists primarily of cessation of bisphosphonate therapy and partial weightbearing activity, and has been proven to be effective in some cohorts[53]. Any nutritional deficiencies should be investigated and appropriately corrected, most notably dietary calcium and vitamin D[11]. More recently, there has been some conflicting evidence surrounding the use of teriparatide in patients with bisphosphonate-associated atypical femoral fractures[54]. It is a recombinant form of parathyroid hormone, and is thought to selectively target bone turnover suppression that occurs as a result of prolonged bisphosphonate use. Whilst some of the evidence is promising, there are also case reports suggesting an absence of this desired effect[55]. Therefore, further investigation is warranted prior to the routine prescription of teriparatide.

Operative fixation

Due to the paucity of evidence for the management of atypical femoral fractures, currently there is no established treatment guidelines for either complete or incomplete fractures. There is agreement in the literature that nonoperative management of bisphosphonate-associated femoral fractures conveys poor outcomes [56,57]. Therefore, it is generally accepted that the current preferred method for first-line management of complete atypical femoral fractures is surgical fixation with a device(s) that can withstand full body loading for a prolonged period to allow bony union. Cephalomedullary nailing, biomechanically gives the most favourable loading properties with on-axis fixation and co-linear strain (Figure 2)[58,59]. Other methods such as plate fixation have been used, usually due to the anatomical location of the fracture but suffer from off-axis fixation and differing strains patterns which can lead
to failure. There is evidence that fractures managed with plate fixation are at greater risk of requiring revision compared with cephalomedullary nailing (31.3% vs 12.9% respectively) [57]. Newer techniques advocate the use of both modalities as it gives the plate advantage of best reducing the fracture and compressing the lateral cortex which has failed in tension with the support of the intramedullary nail to stabilise an atypical fracture with increased ability to load-share, and a reduced bending moment across the fracture site [58,60] (Figure 3). With either fixation technique, however, it is important to avoid fixing the fracture in varus and the operating surgeon should consider creating a small osteotomy along the lateral cortex to remove the pathological bone and best restore the anatomical alignment [50,61].

The evidence base for the management of incomplete atypical femoral fractures is unclear. It has been shown that up to 28.3% of these develop into complete fractures within six months of their detection [62]. Concerning signs include functional pain and a visible transverse fracture line on plain radiographs extending > 50% of the lateral cortex. The rationale behind performing a prophylactic operation on an incomplete atypical femoral fracture is two-fold: progression to complete fracture is prevented and hospital stay is reduced [63]. In addition, the success rate of operative management of complete atypical femoral fractures is reduced by almost 50% when compared with that of incomplete fractures [64]. However, the authors of this study advocate that surgical management for patients presenting with incomplete bisphosphonate-related atypical femoral fractures should be reserved for patients with persistent pain, refractory to nonoperative management or progressive radiographic lesions. There is also recent evidence that prophylactic repair of the contralateral limb may be cost-effective in the treatment of patients presenting with atypical femoral fractures [65].

The literature suggests that operative management of atypical fractures is more challenging than that of typical femoral fractures, necessitating a greater level of surgical expertise and technique [61]. Atypical femoral fracture repair has also been found to have an increased incidence of iatrogenic intraoperative fractures, as well as a higher implant failure rate [66]. The general consensus in the literature is that further large-scale prospective studies are required to evaluate both the outcomes of surgical and conservative management of bisphosphonate-related atypical femoral fractures, as well as trials comparing outcomes from cephalomedullary nailing and other methods of fracture repair in this cohort.

Fracture healing using bone graft in this complex group of patients is an area of consideration to the surgeon. Pathologic by nature, bisphosphonate related atypical femoral fractures are due to chronic osteoclast inhibition, resulting in a site on the femur of reduced remodelling and sclerosis. Autologous bone grafting or bone marrow aspirate may restore the normal bone homeostasis. Currently, the literature is limited in regards to the theoretical benefits. A report by the American Society for Bone and Mineral research found limited evidence to suggest the chronic suppression
of osteoclasts may affect the efficacy of bone grafting at the fracture site\[11\]. Conversely, a study showed no decrease in bone formation after transiliac crest grafting in a similar patient population\[67\]. This shows that further research is required regarding femoral fractures improving time to fracture union.

**Complications and considerations specific to atypical femoral fractures**

Some of the literature reveals favourable outcomes following surgical repair of the atypical femoral fractures, with a reported 95.7% successfully healing without the need of a further operation\[37\]. However, a multicentre review with a greater study population found that 12.6% of atypical femoral fracture repair required revision surgery\[57\]. This is higher than the revision rate for typical femoral fracture repair, which is reported in the literature as 4.7%\[68\]. However, it must be noted that the median ages in these two patient populations vary widely, as patients receiving bisphosphonate therapy skew the median age in this cohort upwards. There are numerous proposed mechanisms for the difference in rates of revision surgery between atypical and typical femoral fracture repair. The primary explanation is that of delayed healing following operative management of an atypical femoral fracture. The mean time to heal following primary repair of atypical fracture by means of cephalomedullary nailing was 10.7 mo\[69\]. This may be related to impaired bone remodelling as a result of bisphosphonate use\[11\]. Although, interestingly, in a review where data regarding preoperative bisphosphonate use was readily available, there was no difference in time to healing when comparing those who had prior treatment with bisphosphonate use for greater than five years and those who had not ($P > 0.05$) \[57\].

A consideration unique to atypical femoral fractures is the incidence of contralateral pathology in those who present after bisphosphonate therapy. There is variation in the reported incidence of contralateral pathology in this population, ranging from approximately 22%\[70\] to 62.9%\[71\]. Regardless, there is evidence enough to suggest routine imaging of the contralateral side in the presence of prodromal pain.

**CONCLUSION**

Bisphosphonates are integral to the treatment of osteoporosis, although there is a particular association with atypical femoral fractures. Although causation between bisphosphonates and atypical fractures is yet to be demonstrated, there is a growing evidence base to suggest a higher predilection of atypical femoral fractures in patients who take bisphosphonates\[14\]. As we encounter a growing co-morbid elderly population, the prevalence of this fracture type will likely increase. Therefore, it is imperative clinicians continue to be attentive of atypical femoral fractures. This can, in part, be done by screening and requesting plain film radiographs, CT scans and DEXA imaging modalities for identification of incomplete or impending fractures. The evidence for the management of complete atypical femoral fractures suggests cephalomedullary nailing to be a favourable compared to plate fixation, in regards to
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likelihood for revision[58,60]. However, it is important to appreciate that the anatomical location and patient factors may not always allow for this. A common subset of atypical femoral fractures are incomplete. Within this population, there is evidence to suggest a significant proportion go on to suffer complete fractures[62]. Therefore, prophylactic cephalomedullary nailing has been suggested in clinically symptomatic patients and visible transverse fracture lines on plain radiographs extending > 50% of the lateral cortex. This has been shown to be a cost effective means of reducing the burden of complete fractures on hospitals. However, surgical fixation in this population does not come without risk and meaningful dialogue with the patients is suggested to individualise treatment decisions in each case.

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