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WJO mainly publishes articles reporting research results and findings obtained in the field of orthopedics and covering a wide range of topics including arthroscopy, bone trauma, bone tumors, hand and foot surgery, joint surgery, orthopedic trauma, osteoarthropathy, osteoporosis, pediatric orthopedics, spinal diseases, spine surgery, and sports medicine.

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MINIREVIEWS

Current concepts in the management of bisphosphonate associated atypical femoral fractures

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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

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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

Core Tip: Bisphosphates are a class of drugs used as the mainstay of treatment for osteoporosis. 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. At the point of presentation of an atypical femoral fracture, bisphosphonate should be discontinued. Currently there is no established treatment guidelines for either complete or incomplete fractures. The evidence suggests that cephalomedullary nailing of the fracture has lower revision rates.

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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

pharmokinetics 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 [5].

Currently the National Institute of Clinical Excellence[7] 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[8]. 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[9].

Recognised side effects of bisphosphonate use include gastrointestinal irritation, musculoskeletal pain, osteonecrosis of the jaw, and more recently recognised, atypical femoral fractures[6]. 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 zolendronic 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[10].

ATYPICAL FEMORAL FRACTURES

Atypical femoral fractures are insufficiency fractures that can be related to bisphosphonate use and are identified by major and minor criteria[11] (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[11,12]) 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 [13]. 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[14]. 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[15].

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 bisphosphonate therapy, most notably GGPS1[28]. Other variants have been identified to predispose individuals to atypical fractures, irrespective of pharmacological therapy

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.

[29]. 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.

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-resporptive properties, thus providing a "holiday" from bisphsphonates 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

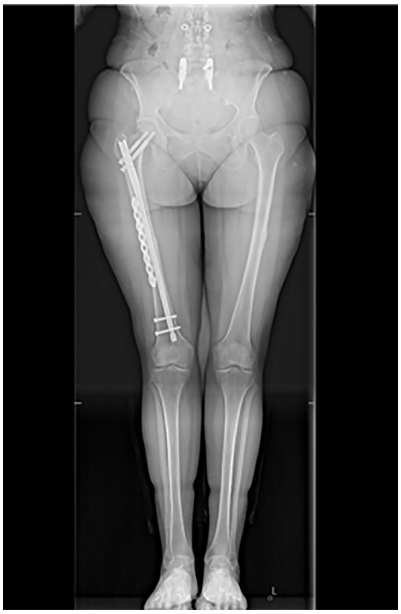

Figure 2 Plain radiograph illustrating fixation of an atypical bisphosphonate associated fracture and beaking on the contralateral limb at the same level.

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

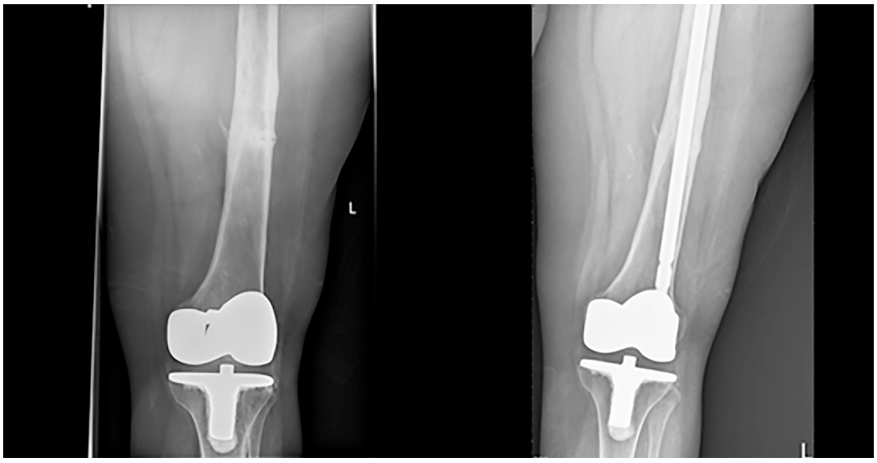

Figure 3 Plain radiographs of the "dreaded lucent line" and distal unlocked intramedullary stabilisation to minimise the stress riser around a knee replacement.

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

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.

REFERENCES

1 **World Health Organisation**. WHO Scientific Group on the Assessment of Osteoporosis at Primary Health Care Level 2004

2 **National Institute for Health and Care Excellence**. Osteoporosis - prevention of fragility fractures 2020. Available from: https://cks.nice.org.uk/topics/osteoporosis-prevention-of-fragility-fractures/

3 **Dempster DW**. Osteoporosis and the burden of osteoporosis-related fractures. *Am J Manag Care* 2011; **17** Suppl 6: S164-S169 [PMID: 21761955 DOI: 10.1007/s00198-002-1313-z]

4 **Khan AA**, Kaiser S. Atypical femoral fracture. *CMAJ* 2017; **189**: E542 [PMID: 28396331 DOI: 10.1503/cmaj.160450]

5 **Drake MT**, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc* 2008; **83**: 1032-1045 [PMID: 18775204 DOI: 10.4065/83.9.1032]

6 **Maraka S**, Kennel KA. Bisphosphonates for the prevention and treatment of osteoporosis. *BMJ* 2015; **351**: h3783 [PMID: 26333528 DOI: 10.1136/bmj.h3783]

7 **National Institute for Health and Care Excellence**. Bisphosphonates for treating osteoporosis. 2017. Available from: https://www.nice.org.uk/guidance/ta464/resources/bisphosphonates-for-treating-osteoporosis

8 **Kanis JA**, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008; **19**: 385-397 [PMID: 18292978 DOI: 10.1007/s00198-007-0543-5]

9 **Wells GA**, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev* 2008; CD001155 [PMID: 18253985 DOI: 10.1002/14651858.CD001155.pub2]

10 **Black DM**, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR; HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; **356**: 1809-1822 [PMID: 17476007 DOI: 10.1056/NEJMoa067312]

11 **Shane E**, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster DW, Ebeling PR, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Lane JM, McKiernan F, McKinney R, Ng A, Nieves J, O'Keefe R, Papapoulos S, Howe TS, van der Meulen MC, Weinstein RS, Whyte MP. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2014; **29**: 1-23 [PMID: 23712442 DOI: 10.1002/jbmr.1998]

12 **Neviaser AS**, Lane JM, Lenart BA, Edobor-Osula F, Lorich DG. Low-energy femoral shaft fractures associated with alendronate use. *J Orthop Trauma* 2008; **22**: 346-350 [PMID: 18448990 DOI: 10.1097/BOT.0b013e318172841c]

13 **Abrahamsen B**, Eiken PA, Eastell R. Subtrochanteric and diaphyseal fractures in patients during long-term alendronate treatment: Expanded and extended national register based cohort study. *Bone* 2010; **47** (Suppl 1): S62-S3 [DOI: 10.1016/j.bone.2010.04.120]

14 **Schilcher J**, Michaëlsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med* 2011; **364**: 1728-1737 [PMID: 21542743 DOI: 10.1056/NEJMoa1010650]

15 **Black DM**, Geiger EJ, Eastell R, Vittinghoff E, Li BH, Ryan DS, Dell RM, Adams AL. Atypical Femur Fracture Risk versus Fragility Fracture Prevention with Bisphosphonates. *N Engl J Med* 2020; **383**: 743-753 [PMID: 32813950 DOI: 10.1056/NEJMoa1916525]

16 **Balach T**, Baldwin PC, Intravia J. Atypical Femur Fractures Associated With Diphosphonate Use. *J Am Acad Orthop Surg* 2015; **23**: 550-557 [PMID: 26195566 DOI: 10.5435/JAAOS-D-14-00024]

17 **Saita Y**, Ishijima M, Kaneko K. Atypical femoral fractures and bisphosphonate use: current evidence and clinical implications. *Ther Adv Chronic Dis* 2015; **6**: 185-193 [PMID: 26137208 DOI: 10.1177/2040622315584114]

18 **Tonino RP**, Meunier PJ, Emkey R, Rodriguez-Portales JA, Menkes CJ, Wasnich RD, Bone HG, Santora AC, Wu M, Desai R, Ross PD. Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. Phase III Osteoporosis Treatment Study Group. *J Clin Endocrinol Metab* 2000; **85**: 3109-3115 [PMID: 10999794 DOI: 10.1210/jcem.85.9.6777]

19 **Liberman UA**, Weiss SR, Bröll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW

Jr, Dequeker J, Favus M. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med* 1995; **333**: 1437-1443 [PMID: 7477143 DOI: 10.1056/NEJM199511303332201]

20 **Odvina CV**, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab* 2005; **90**: 1294-1301 [PMID: 15598694 DOI: 10.1210/jc.2004-0952]

21 **Russell RG**, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int* 2008; **19**: 733-759 [PMID: 18214569 DOI: 10.1007/s00198-007-0540-8]

22 **Steiniche T**, Hasling C, Charles P, Eriksen EF, Melsen F, Mosekilde L. The effects of etidronate on trabecular bone remodeling in postmenopausal spinal osteoporosis: a randomized study comparing intermittent treatment and an ADFR regime. *Bone* 1991; **12**: 155-163 [PMID: 1910957 DOI: 10.1016/8756-3282(91)90038-k]

23 **Mashiba T**, Turner CH, Hirano T, Forwood MR, Johnston CC, Burr DB. Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. *Bone* 2001; **28**: 524-531 [PMID: 11344052 DOI: 10.1016/s8756-3282(01)00414-8]

24 **Hirano T**, Turner CH, Forwood MR, Johnston CC, Burr DB. Does suppression of bone turnover impair mechanical properties by allowing microdamage accumulation? *Bone* 2000; **27**: 13-20 [PMID: 10865204 DOI: 10.1016/s8756-3282(00)00284-2]

25 **Boivin G**, Meunier PJ. Changes in bone remodeling rate influence the degree of mineralization of bone. *Connect Tissue Res* 2002; **43**: 535-537 [PMID: 12489211 DOI: 10.1080/03008200290000934]

26 **Akkus O**, Polyakova-Akkus A, Adar F, Schaffler MB. Aging of microstructural compartments in human compact bone. *J Bone Miner Res* 2003; **18**: 1012-1019 [PMID: 12817753 DOI: 10.1359/jbmr.2003.18.6.1012]

27 **Allen MR**, Burr DB. Bisphosphonate effects on bone turnover, microdamage, and mechanical properties: what we think we know and what we know that we don't know. *Bone* 2011; **49**: 56-65 [PMID: 20955825 DOI: 10.1016/j.bone.2010.10.159]

28 **Roca-Ayats N**, Balcells S, Garcia-Giralt N, Falcó-Mascaró M, Martínez-Gil N, Abril JF, Urreizti R, Dopazo J, Quesada-Gómez JM, Nogués X, Mellibovsky L, Prieto-Alhambra D, Dunford JE, Javaid MK, Russell RG, Grinberg D, Díez-Pérez A. GGPS1 Mutation and Atypical Femoral Fractures with Bisphosphonates. *N Engl J Med* 2017; **376**: 1794-1795 [PMID: 28467865 DOI: 10.1056/NEJMc1612804]

29 **Funck-Brentano T**, Ostertag A, Debiais F, Fardellone P, Collet C, Mornet E, Cohen-Solal M. Identification of a p.Arg708Gln variant in COL1A2 in atypical femoral fractures. *Joint Bone Spine* 2017; **84**: 715-718 [PMID: 28017821 DOI: 10.1016/j.jbspin.2016.11.014]

30 **Kharazmi M**, Michaëlsson K, Schilcher J, Eriksson N, Melhus H, Wadelius M, Hallberg P. A Genome-Wide Association Study of Bisphosphonate-Associated Atypical Femoral Fracture. *Calcif Tissue Int* 2019; **105**: 51-67 [PMID: 31006051 DOI: 10.1007/s00223-019-00546-9]

31 **Yoo H**, Cho Y, Park Y, Ha S. Lateral Femoral Bowing and the Location of Atypical Femoral Fractures. *Hip Pelvis* 2017; **29**: 127-132 [PMID: 28611964 DOI: 10.5371/hp.2017.29.2.127]

32 **Crossley K**, Bennell KL, Wrigley T, Oakes BW. Ground reaction forces, bone characteristics, and tibial stress fracture in male runners. *Med Sci Sports Exerc* 1999; **31**: 1088-1093 [PMID: 10449008 DOI: 10.1097/00005768-199908000-00002]

33 **Sasaki S**, Miyakoshi N, Hongo M, Kasukawa Y, Shimada Y. Low-energy diaphyseal femoral fractures associated with bisphosphonate use and severe curved femur: a case series. *J Bone Miner Metab* 2012; **30**: 561-567 [PMID: 22610061 DOI: 10.1007/s00774-012-0358-0]

34 **Kennel KA**, Drake MT. Adverse effects of bisphosphonates: implications for osteoporosis management. *Mayo Clin Proc* 2009; **84**: 632-7; quiz 638 [PMID: 19567717 DOI: 10.1016/S0025-6196(11)60752-0]

35 **Porrino JA Jr**, Kohl CA, Taljanovic M, Rogers LF. Diagnosis of proximal femoral insufficiency fractures in patients receiving bisphosphonate therapy. *AJR Am J Roentgenol* 2010; **194**: 1061-1064 [PMID: 20308511 DOI: 10.2214/AJR.09.3383]

36 **Adams AL**, Xue F, Chantra JQ, Dell RM, Ott SM, Silverman S, Giaconi JC, Critchlow C. Sensitivity and specificity of radiographic characteristics in atypical femoral fractures. *Osteoporos Int* 2017; **28**: 413-417 [PMID: 27766369 DOI: 10.1007/s00198-016-3809-y]

37 **Lee KJ**, Yoo JJ, Oh KJ, Yoo JH, Rhyu KH, Nam KW, Suh DH. Surgical outcome of intramedullary nailing in patients with complete atypical femoral fracture: A multicenter retrospective study. *Injury* 2017; **48**: 941-945 [PMID: 28274470 DOI: 10.1016/j.injury.2017.02.036]

38 **Lee KJ**, Min BW, Bae KC, Cho CH, Lee SW, Kim BS. Progression of Asymptomatic Contralateral Femur in Patients with Complete Atypical Femoral Fracture, According to Initial Radiographic Findings. *J Bone Joint Surg Am* 2021; **103**: 123-130 [PMID: 33476100 DOI: 10.2106/JBJS.20.00807]

39 **Ahovuo JA**, Kiuru MJ, Visuri T. Fatigue stress fractures of the sacrum: diagnosis with MR imaging. *Eur Radiol* 2004; **14**: 500-505 [PMID: 14576960 DOI: 10.1007/s00330-003-1989-2]

40 **Kharwadkar N**, Mayne B, Lawrence JE, Khanduja V. Bisphosphonates and atypical subtrochanteric fractures of the femur. *Bone Joint Res* 2017; **6**: 144-153 [PMID: 28288986 DOI: 10.1302/2046-3758.63.BJR-2016-0125.R1]

41 **McKenna MJ**, van der Kamp S, Heffernan E, Hurson C. Incomplete atypical femoral fractures:

assessing the diagnostic utility of DXA by extending femur length. *J Clin Densitom* 2013; **16**: 579-583 [PMID: 23896493 DOI: 10.1016/j.jocd.2013.06.004]

42 **Png MA**, Koh JS, Goh SK, Fook-Chong S, Howe TS. Bisphosphonate-related femoral periosteal stress reactions: scoring system based on radiographic and MRI findings. *AJR Am J Roentgenol* 2012; **198**: 869-877 [PMID: 22451554 DOI: 10.2214/AJR.11.6794]

43 **Probst S**, Rakheja R, Stern J. Atypical bisphosphonate-associated subtrochanteric and femoral shaft stress fractures: diagnostic features on bone scan. *Clin Nucl Med* 2013; **38**: 397-399 [PMID: 23478849 DOI: 10.1097/RLU.0b013e318286bfb6]

44 **Haj-Mirzaian A**, Eng J, Khorasani R, Raja AS, Levin AS, Smith SE, Johnson PT, Demehri S. Use of Advanced Imaging for Radiographically Occult Hip Fracture in Elderly Patients: A Systematic Review and Meta-Analysis. *Radiology* 2020; **296**: 521-531 [PMID: 32633673 DOI: 10.1148/radiol.2020192167]

45 **Vasikaran S**, Eastell R, Bruyère O, Foldes AJ, Garnero P, Griesmacher A, McClung M, Morris HA, Silverman S, Trenti T, Wahl DA, Cooper C, Kanis JA; IOF-IFCC Bone Marker Standards Working Group. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int* 2011; **22**: 391-420 [PMID: 21184054 DOI: 10.1007/s00198-010-1501-1]

46 **Matos MA**, Tannuri U, Guarniero R. The effect of zoledronate during bone healing. *J Orthop Traumatol* 2010; **11**: 7-12 [PMID: 20169393 DOI: 10.1007/s10195-010-0083-1]

47 **Amanat N**, McDonald M, Godfrey C, Bilston L, Little D. Optimal timing of a single dose of zoledronic acid to increase strength in rat fracture repair. *J Bone Miner Res* 2007; **22**: 867-876 [PMID: 17371160 DOI: 10.1359/jbmr.070318]

48 **Im GI**, Qureshi SA, Kenney J, Rubash HE, Shanbhag AS. Osteoblast proliferation and maturation by bisphosphonates. *Biomaterials* 2004; **25**: 4105-4115 [PMID: 15046901 DOI: 10.1016/j.biomaterials.2003.11.024]

49 **Anagnostis P**, Paschou SA, Mintziori G, Ceausu I, Depypere H, Lambrinoudaki I, Mueck A, Pérez-López FR, Rees M, Senturk LM, Simoncini T, Stevenson JC, Stute P, Trémollieres FA, Goulis DG. Drug holidays from bisphosphonates and denosumab in postmenopausal osteoporosis: EMAS position statement. *Maturitas* 2017; **101**: 23-30 [PMID: 28539165 DOI: 10.1016/j.maturitas.2017.04.008]

50 **Jones CB**. Atypical Femoral Fractures: An Orthopaedic Surgeon's Perspective. *Curr Transl Geriatr Exp Gerontol Rep* 2013; **2**: 91-98 [DOI: 10.1007/s13670-013-0045-6]

51 **Dunford JE**, Thompson K, Coxon FP, Luckman SP, Hahn FM, Poulter CD, Ebetino FH, Rogers MJ. Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. *J Pharmacol Exp Ther* 2001; **296**: 235-242 [PMID: 11160603]

52 **Dell R**, Greene D, Tran D. Stopping bisphosphonate treatment decreases the risk of having a second atypical femur fracture. In: American Academy of Orthopaedic Surgeons 2012 Annual Meeting; 2012 Feb 7-11; San Francisco, United States

53 **Cermak K**, Shumelinsky F, Alexiou J, Gebhart MJ. Case reports: subtrochanteric femoral stress fractures after prolonged alendronate therapy. *Clin Orthop Relat Res* 2010; **468**: 1991-1996 [PMID: 20020334 DOI: 10.1007/s11999-009-1192-0]

54 **Im GI**, Lee SH. Effect of Teriparatide on Healing of Atypical Femoral Fractures: A Systemic Review. *J Bone Metab* 2015; **22**: 183-189 [PMID: 26713309 DOI: 10.11005/jbm.2015.22.4.183]

55 **Nguyen HH**, Milat F, Ebeling PR. A new contralateral atypical femoral fracture despite sequential therapy with teriparatide and strontium ranelate. *Bone Rep* 2017; **6**: 34-37 [PMID: 28377979 DOI: 10.1016/j.bonr.2017.01.002]

56 **Divan V**, Rao SD, Dhaliwal R. Detection and management of atypical femur fractures. *Curr Opin Endocrinol Diabetes Obes* 2019; **26**: 283-290 [PMID: 31592780 DOI: 10.1097/MED.0000000000000505]

57 **Koh A**, Guerado E, Giannoudis PV. Atypical femoral fractures related to bisphosphonate treatment: issues and controversies related to their surgical management. *Bone Joint J* 2017; **99-B**: 295-302 [PMID: 28249967 DOI: 10.1302/0301-620X.99B3.BJJ-2016-0276.R2]

58 **Githens M**, Garner MR, Firoozabadi R. Surgical Management of Atypical Femur Fractures Associated With Bisphosphonate Therapy. *J Am Acad Orthop Surg* 2018; **26**: 864-871 [PMID: 30256339 DOI: 10.5435/JAAOS-D-16-00717]

59 **Bogdan Y**, Tornetta P 3rd, Einhorn TA, Guy P, Leveille L, Robinson J, Bosse MJ, Haines N, Horwitz D, Jones C, Schemitsch E, Sagi C, Thomas B, Stahl D, Ricci W, Brady M, Sanders D, Kain M, Higgins TF, Collinge C, Kottmeier S, Friess D. Healing Time and Complications in Operatively Treated Atypical Femur Fractures Associated With Bisphosphonate Use: A Multicenter Retrospective Cohort. *J Orthop Trauma* 2016; **30**: 177-181 [PMID: 26709814 DOI: 10.1097/BOT.0000000000000516]

60 **Giannoudis PV**, Ahmad MA, Mineo GV, Tosounidis TI, Calori GM, Kanakaris NK. Subtrochanteric fracture non-unions with implant failure managed with the "Diamond" concept. *Injury* 2013; **44** Suppl 1: S76-S81 [PMID: 23351877 DOI: 10.1016/S0020-1383(13)70017-2]

61 **Larsen MS**, Schmal H. The enigma of atypical femoral fractures: A summary of current knowledge. *EFORT Open Rev* 2018; **3**: 494-500 [PMID: 30305933 DOI: 10.1302/2058-5241.3.170070]

62 **Min BW**, Koo KH, Park YS, Oh CW, Lim SJ, Kim JW, Lee KJ, Lee YK. Scoring System for Identifying Impending Complete Fractures in Incomplete Atypical Femoral Fractures. *J Clin Endocrinol Metab* 2017; **102**: 545-550 [PMID: 27802096 DOI: 10.1210/jc.2016-2787]

63 **Banffy MB**, Vrahas MS, Ready JE, Abraham JA. Nonoperative versus prophylactic treatment of bisphosphonate-associated femoral stress fractures. *Clin Orthop Relat Res* 2011; **469**: 2028-2034 [PMID: 21350886 DOI: 10.1007/s11999-011-1828-8]

64 **Egol KA**, Park JH, Prensky C, Rosenberg ZS, Peck V, Tejwani NC. Surgical treatment improves clinical and functional outcomes for patients who sustain incomplete bisphosphonate-related femur fractures. *J Orthop Trauma* 2013; **27**: 331-335 [PMID: 22986315 DOI: 10.1097/BOT.0b013e31827240ae]

65 **Jiang SY**, Kaufman DJ, Chien BY, Longoria M, Shachter R, Bishop JA. Prophylactic Fixation Can Be Cost-effective in Preventing a Contralateral Bisphosphonate-associated Femur Fracture. *Clin Orthop Relat Res* 2019; **477**: 480-490 [PMID: 30394950 DOI: 10.1097/CORR.0000000000000545]

66 **Prasarn ML**, Ahn J, Helfet DL, Lane JM, Lorich DG. Bisphosphonate-associated femur fractures have high complication rates with operative fixation. *Clin Orthop Relat Res* 2012; **470**: 2295-2301 [PMID: 22669553 DOI: 10.1007/s11999-012-2412-6]

67 **Jamal SA**, Dion N, Ste-Marie LG. Atypical femoral fractures and bone turnover. *N Engl J Med* 2011; **365**: 1261-1262 [PMID: 21991914 DOI: 10.1056/NEJMc1107029]

68 **Wolinsky PR**, McCarty E, Shyr Y, Johnson K. Reamed intramedullary nailing of the femur: 551 cases. *J Trauma* 1999; **46**: 392-399 [PMID: 10088839 DOI: 10.1097/00005373-199903000-00007]

69 **Cho JW**, Oh CW, Leung F, Park KC, Wong MK, Kwek E, Kim HJ, Oh JK. Healing of Atypical Subtrochanteric Femur Fractures After Cephalomedullary Nailing: Which Factors Predict Union? *J Orthop Trauma* 2017; **31**: 138-145 [PMID: 28009615 DOI: 10.1097/BOT.0000000000000743]

70 **Dell RM**, Adams AL, Greene DF, Funahashi TT, Silverman SL, Eisemon EO, Zhou H, Burchette RJ, Ott SM. Incidence of atypical nontraumatic diaphyseal fractures of the femur. *J Bone Miner Res* 2012; **27**: 2544-2550 [PMID: 22836783 DOI: 10.1002/jbmr.1719]

71 **Schilcher J**, Aspenberg P. Incidence of stress fractures of the femoral shaft in women treated with bisphosphonate. *Acta Orthop* 2009; **80**: 413-415 [PMID: 19568963 DOI: 10.3109/17453670903139914]

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