REVIEW ARTICLE

Skeletal complications of bisphosphonate use: what the radiologist should know

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ABSTRACT. Bisphosphonates are widely used for prevention of fractures in patients at risk, mainly in the presence of osteoporosis and bone metastases. A number of adverse effects of prolonged bisphosphonate treatment have emerged. We would like to highlight the skeletal complications from which a radiologist may be the first healthcare professional to recognise the association with bisphosphonate therapy. We illustrate these complications (namely osteonecrosis of the jaw and less well-known atypical femoral shaft fractures), presenting radiological findings in our patients. Recommendations for safer use of bisphosphonates are included in the conclusion of our review.

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Bisphosphonates are non-metabolic synthetic analogues of pyrophosphate and have a significant effect on bone turnover, inhibiting osseous resorption by suppressing osteoclast activity [1, 2]. This results in bone microarchitecture modifications. As they are metabolically inactive, they bind to bone, creating a reservoir that remains even after discontinuation of treatment [3]. Studies have shown antifracture efficacy to persist for 1–2 years following discontinuation of alendronate, and between 3 and 5 years following risendronate use [4].

Bisphosphonates are the treatment of choice in conditions characterised by an increase in bone resorption. In the UK they are used in the treatment of lytic metastases arising from breast cancer, osteoporosis, hypercalcaemia secondary to malignancy, Paget's disease of bone and multiple myeloma [5]. Less well-known indications include osteogenesis imperfecta and juvenile idiopathic arthritis. Worldwide, their indications are extending to include lytic metastases from other solid tumours [6]. Two forms of the drug are used: intravenous (iv) and oral. In 2009–10 alone over 1 million people in the UK were prescribed bisphosphonates and over 6.5 million prescriptions were issued [7]. In the USA, an estimated 30 million prescriptions for bisphosphonates are written every year [8]. There is abundant evidence in the literature extolling the benefits of bisphosphonate use, and indeed these are multiple and often provide significant increases in quality of life for patients. The number of patients needed to be treated with bisphosphonates for 3 years to prevent 1 vertebral and 1 hip fracture are 14 and 91, respectively [9]. There are, however, several potential side-effects relating to their use. These include gastrointestinal discomfort, influenza-like illness (due to acute phase reaction), renal complications (rare even in

high-dose iv treatment) and a theoretical link to acceleration of coronary artery disease.

More importantly for a radiologist, there is increasing evidence to suggest a separate subset of complications affecting the skeleton. Although they are well described in metabolic and orthopaedic journals, they are less well known to the radiological community. These are complications that might be expected from the mechanism of action of bisphosphonates, and, in view of their rising usage, are likely to be seen with increasing frequency. In this article we describe the skeletal complications of bisphosphonate use and the radiographic findings of each.

Bisphosphonate-related osteonecrosis of the jaw

Definition

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a painful destructive process, which is distinguishable from other impaired healing conditions by the following features:

- current or previous treatment with a bisphosphonate;
- exposed bone in the maxillofacial region that has persisted for more than 8 weeks; and
- no history of radiation therapy to the jaws [10].

Causes, predisposing factors and histopathological features

The exact underlying aetiology of BRONJ is unknown. It tends to affect the mandible rather than the maxilla, although both jaws can be affected simultaneously. The maxilla is thought to be relatively spared because of its increased vascularity.

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The suggested mechanism is via the inhibition of bone turnover. Bisphosphonates are thought to incorporate at sites of high osseous turnover (e.g. the mandible, where marked suppression of bone metabolism results in accumulation of physiological microdamage, occurring as a result of mastication).

The thin mucosa and periosteum covering the jaws are easily breached by infection (oral flora) or local trauma (dental procedures) and the presence of either micro-trauma, infection or iatrogenic damage can increase demand for osseous repair beyond the capacity of the newly hypodynamic bone, resulting in local osteonecrosis. Commonly, oral flora such as *Actinomyces israelii* are found colonising biopsy specimens of BRONJ; however, while some lesions have responded to antibiotic therapy it is unclear whether the organisms are causative or incidental [11].

Generally there is no classic histopathological appearance for BRONJ. Specimens from exposed bone often show non-vital bone with rough margins and empty lacunae, consistent with necrosis. Unexposed bone specimens contain hypervascular fibrotic tissue with inflammatory infiltrates filling the trabecular space, which is often seen in chronic osteomyelitis. Fungal contamination is common in exposed specimens [12].

Incidence and prevalence

The estimated risk of BRONJ in patients receiving anti-resorptive therapy is rare. The occurrence in oral bisphosphonate use is estimated to be between 1 in 10 000 and 1 in 100 000 patient years, with more frequent occurrences in females and age groups older than 60 years [13, 14].

The majority of reported cases of BRONJ (approximately 95%) are associated with iv bisphosphonate therapy in the management of metastatic bone disease (often with doses up to 12 times greater than those used in oral treatment regimes for osteoporosis) [14, 15]. Woo et al [16], in a systematic review of 368 published cases of BRONJ, suggested a prevalence of between 6% and 10% for patients on iv therapy for metastatic bone disease [16]. There is also evidence to suggest an association between subtypes of bisphosphonates and risk. Pamidronate (containing an aminoterminal group) was less commonly associated with osteonecrosis of the jaw than zoledronate (containing a nitrogen side-chain) [17]. In addition, the chemotherapeutic agents and steroids taken by many of the patients receiving bisphosphonate treatment will almost certainly contribute to impaired wound healing, and so exacerbate osteonecrosis formation.

Symptomatology

The diagnosis of BRONJ is often clinical, with a relatively consistent symptomatology. However, it is frequently detected late as the patient becomes symptomatic only after osteonecrosis is well established. It usually presents with pain and/or a non-healing extraction socket. This leads to exposed, non-vital bone with subsequent sequestrum formation and associated swelling or purulent discharge.

(a)

(b)

Figure 1. (a) Female patient diagnosed with metastatic breast cancer. Increasing pain following left lower premolar extractions 5 years after commencing on intravenous pamidronate. Photograph of exposed bone at presentation post extraction. (b) Two orthopantomograms 1 year apart showing lytic process developing at the site of tooth extraction (arrows).

Sometimes it can be recognised solely by the exposed bone (Figure 1a).

Radiological findings

As BRONJ occurs most commonly in oncology patients receiving iv bisphosphonate therapy for bone

Figure 2. Male patient on high-dose intravenous pamidronate for hypercalcaemia of prostatic malignancy. The orthopantomogram shows subtle lysis and sclerosis in the left lower premolar region post extraction (arrow).

metastases it is important to differentiate this from neoplastic invasion, osteomyelitis and radiotherapy-induced osteonecrosis. This is an important distinction as similar radiographic appearances can be seen following radiotherapy (therefore a history of previous head and neck irradiation needs to be excluded before a diagnosis of BRONJ can be made). As unnecessary bone biopsy causes local osseous damage (and can exacerbate osteonecrosis) it is to be avoided if possible. In general, most institutions use the presence of 8 weeks of exposed bone in a bisphosphonate-treated patient without a history of radiotherapy as diagnostic of BRONJ [3, 14].

The radiographic appearances are non-specific at both anatomical and functional imaging. The bone changes may be mixed, predominantly sclerotic or predominantly lytic.

Radiograph/CT

The early imaging findings in BRONJ seem to be focal medullary sclerosis with poor corticomedullary differentiation and involvement of the inferior alveolar canal, which is clinically associated with tooth loosening. Delayed socket healing following tooth extraction should

Figure 3. Male patient (same patient as in Figure 2). T_1 weighted axial image showing abnormal low signal change in the left and central mandible with subtle low signal (oedema) in the adjacent soft tissue (arrow).

Figure 4. Male patient (same patient as in Figure 2). Short-tau inversion-recovery image at the same level as Figure 3 shows high signal in the adjacent soft tissue (oedema) but variable signal in the mandible (arrow).

Figure 5. Male patient (same patient as in Figure 2). Post-gadolinium axial T_1 weighted image showing areas of abnormal enhancement in the affected mandible and surrounding tissue (arrow).

also raise the possibility of osteonecrosis of the jaw (Figures 1b and 2).

Sequestrum formation, fractures and periosteal reaction are all associated with late disease [3, 13, 17–19]. When the maxilla is involved there may be mucosal thickening in the adjacent sinus with fluid levels or purulent discharge.

Radiographs may appear normal if lesions are <1 cm in diameter and as such multidetector CT (MDCT) is often

required with multiplanar reformats to fully assess the extent of disease involvement. More recently cone-beam CT (CBCT) with three-dimensional reformats has been described as a possible way of improving detection of early BRONJ [20]. A facial bone trauma protocol (slice thickness 1.25 mm, interval 0.75 mm, 120 kV and 350–440 mAs) with multiplanar reconstructions is usually sufficient in most circumstances.

MRI

MRI characteristics are variable, depending on the stage of disease. Typically osteonecrosis of the jaw displays low signal intensity on T_1 weighted (T_1W) sequences, with a more variable pattern on T_2 weighted (T_2W), short-tau inversion-recovery (STIR) and on T_1W sequences post-iv gadolinium. The MRI changes in early disease are not well described in the literature, owing in part to the lack of MRI in early disease. Bisdas et al [18] describe variable T_2W signal generally but they noted focal low T_1W and intermediate/high T_2W signal in the region of the open wound consistent with oedema.

Late-stage disease typically appears similar to the expected histological findings, with unexposed bone displaying high signal on T_2W and STIR sequences compatible with a chronic osteomyelitic pattern, and exposed bone displaying low T_2W /STIR intensity compatible with necrosis. These signal characteristics can be localised to the cortex or extend into the marrow, inferior alveolar canal, adjacent soft tissues and/or the maxillary sinus. Soft tissue involvement is often seen in late-stage disease with high T_2W signal (oedema) and soft tissue enhancement (often extending to the mylohyoid ridge, buccinator muscle and masticator space). This can present as focal, mass-like thickening of the involved muscles, mimicking neoplastic invasion, which can complicate management [18]. Cervical adenopathy, in particular of the submandibular and jugulodigastric chains, is also a common finding on MRI, again complicating matters in oncology patients (Figures 3–6) [21].

In general the MRI findings are non-specific, relating to oedema/inflammation and necrosis. However, when put in clinical context they can accurately evaluate the extent of disease and surrounding soft tissue

Figure 6. Female patient taking aledronic acid (75mg per os per week) for osteoporosis (6 years). Admission radiographs following trivial trauma show a transverse right femoral fracture (asterisk) with a medial uncortical beak (arrows). There is subtle thickening of the lateral cortex in the region of the fracture. She had experienced prodromal pain, but a pelvic radiograph 3 weeks earlier did not include the upper femoral diaphysis.

Table 1. Imaging findings in osteonecrosis of the jaw

Modality	Characteristics
Radiographic	Osteolysis, sclerosis, periosteal reaction, narrowing of the marrow space with sclerosis, fractures, inferior alveolar canal involvement
CT	As above
MRI	
T1W	Usually decreased signal
T2W	Variable; usually intermediate or increased in early disease (oedema), increased or decreased in late disease (oedema vs sclerosis)
STIR	Variable; usually increased signal in early disease (oedema), increased or decreased as disease progresses (oedema vs sclerosis)
T1W post gadolinium	Variable; usually correlates with decreased T1W signal area, but spares low T2W signal sclerosis/sequestrum
^{99m} Tc MDP bone scintigraphy	Occasionally decreased uptake in early disease; increase in uptake in late disease, occasionally with central scar (dependent on lesion size)

MDP, methylene diphosphonate; STIR, short-tau inversion-recovery; T1W, T₁ weighted; T2W, T₂ weighted; ^{99m}Tc, technetium-99m.

involvement, to help in the planning of surgical debridement of intractable cases.

Functional imaging

O’Ryan et al [22] reported an increase in uptake on bone scintigraphy in nearly 66% of patients who subsequently developed clinically overt BRONJ. Rarely, single photon emission CT (SPECT) can help to differentiate between the increased uptake of reactive bone and the decreased uptake of a sequestrum, further increasing diagnostic confidence; however, this is highly dependent on the lesion size [23]. Limited information on the use of fludeoxyglucose (FDG) positron emission tomography (PET) is available. It appears to be sensitive (but not specific) in the assessment of osteonecrosis of the jaw, with the increased uptake of FDG possibly relating to the healing response, surrounding inflammation or superadded infection (Table 1) [24].

Management

The severity of BRONJ has been graded by the American Association of Oral and Maxillofacial Surgeons, and management has been tailored to each grade [10]. Before commencing with iv bisphosphonates, preventative measures are undertaken in patients at risk of developing BRONJ, consisting of oral examination, removal of non-viable teeth, completion of any invasive dental treatment and achievement of optimal orodental health. No such

measures are necessary prior to commencing oral bisphosphonates. Patients who develop symptoms are given antimicrobial oral rinses, systemic antibiotics and have necessary surgical treatment, with removal of necrotic bone fragments without exposing non-affected bone. Following resection or fracture, reconstructive surgery may be undertaken. Hyperbaric oxygen, ozone and laser therapy have all been tried, with variable results.

Case reports of successful use of recombinant human parathyroid hormone, teriparatide, have been published, but no randomised trials are yet available [25]; in the light of opposing cellular and tissue effects of bisphosphonates and teriparatide such a trial would be of interest.

Discontinuation of bisphosphonate therapy is of no benefit in the short term, but may improve the outcome in the long term.

Low-impact atypical femoral fractures

Definition

Atypical femoral fractures are seen predominantly in the proximal third of the shaft just distal to the lesser trochanter; however, they can occur throughout the diaphysis down to the supracondylar region. By definition they occur as a result of minimal or no trauma, usually said to equate to a fall from a standing height or less (whereas 75% of femoral fractures occur as a result of high-impact trauma, and are spiral in nature in more

Table 2. Major and minor criteria in diagnosing atypical femoral fractures

Major criteria	Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare Associated with no trauma or minimal trauma (fall from a standing height or less) Transverse or <30° oblique configuration Non-comminuted Complete fractures extend through both cortices and may be associated with a medial spike Incomplete fractures involve only the lateral cortex
Minor criteria	Localised periosteal reaction of the lateral cortex Generalised increase in cortical thickness of the diaphysis Prodromal symptoms such as dull or aching pain in the groin or thigh Bilateral fractures and symptoms Delayed healing Comorbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) Use of pharmaceutical agents (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors)

than 50%). Characteristically, patients report prodromal symptoms of deep thigh or groin pain. The fracture may be complete or incomplete. Complete fractures are usually transverse with a characteristic medial unicortical "beak". They may also have a slight oblique ($<30^\circ$) orientation [26, 27]. For the diagnosis of an atypical fracture a number of exclusion criteria must be met:

The fracture must not be:

- femoral neck, intertrochanteric or spiral diaphyseal
- associated with a local primary bone tumour
- associated with metastatic bone disease
- periprosthetic.

Both subtypes (complete/incomplete) are commonly associated with a periosteal stress reaction. This is often seen as thickening of the lateral cortex at the fracture site. However, there may also be a more diffuse thickening throughout the affected region [28–32].

A task force commissioned by the American Society for Bone and Mineral Research produced criteria for diagnosing atypical femoral fractures [32]. All of the major criteria need to be met for an atypical femoral fracture. The minor criteria are associated findings from their meta-analysis of the literature (Table 2).

Causes, predisposing factors and histopathological features

Bisphosphonates have a number of effects on bone, as discussed above. The exact aetiology responsible for atypical fractures, however, remains unclear, and no definite causal link has been established. The effects of bisphosphonates on several components of bone are, however, pointing towards their role in atypical femoral fractures.

Collagen

The organic matrix of bone is the critical determinant of its strength. Bisphosphonates are associated with both positive and negative alterations on the formation of bone matrix by changes in both collagen maturity and cross-links. The bone matrix contains both enzymatic and non-enzymatic collagen cross-links, which add to the structural integrity of the matrix [33]. In the short term, bisphosphonates were shown to decrease turnover of enzymatic collagen cross-links, which leads to increased strength. In the longer term, however, they increased non-enzymatic collagen cross-links, reducing bone strength [34, 35].

Bone density distribution

This is a marker of the heterogeneity of the bone matrix. In general the density distribution varies only slightly within cancellous bone in the adult population, corresponding to a mechanical and biological optimum state for stability [35]. A slight change in this heterogeneity, to a more homogeneous distribution, leaves the bone more susceptible to "cracks" and less able to slow the process of microdamage. In reducing bone turnover with bisphosphonates the overall mineralisation is increased, but there seems to be an associated reduction in the heterogeneity of the matrix [36, 37]. This leaves the

bone more susceptible to injury. There is evidence emerging to suggest that this is transient and the distribution returns to a normal state after 5–10 years of treatment [38].

Remodelling

Bone remodelling is a critical mechanism in which bones strengthen and repair themselves in response to stress. Excessive remodelling reduces bone mass and strength by distorting the micro-architecture. Bisphosphonate therapy aims to suppress remodelling to avoid this; however, by reducing remodelling, the ability to repair the microtrauma that occurs on a daily basis is inadvertently reduced, leading to accumulation of damage [39]. This accumulation occurs naturally with ageing (particularly in those over 70 years of age), but occurs more rapidly with bisphosphonate use [40].

Incidence and prevalence

The most up-to-date work, published in 2011 by Park-Wyllie et al [41], showed that when compared with transient bisphosphonate use, treatment for 5 years or longer was associated with an increased risk of atypical femoral shaft fracture (adjusted odds ratio, 2.74; 95% confidence interval, 1.25–6.02). This was, however, weighed up against the reduced risk of typical osteoporotic fractures among women with more than 5 years of bisphosphonate therapy (adjusted odds ratio, 0.76; 95% confidence interval, 0.63–0.93).

Symptomatology

The typical scenario is prodromal pain in the affected limb(s) over several weeks to months prior to presentation with an atypical fracture. This often occurs following normal activity with no significant trauma.

Radiological findings

The radiological findings are now well described. The fractures are transverse (or $<30^\circ$ oblique) diaphyseal fractures occurring in a region of underlying cortical thickening. The thickening is often seen on the acute radiographs; however, it is also usually present prior to injury on images acquired because of the persistent pain.

The fracture itself has a characteristic medial unicortical beak, with no features to suggest an underlying lytic process [30].

Radiograph/CT

If these are available prior to the diagnosis of atypical femoral fracture, the findings are variable, with possible thickening of the cortex. However, many radiographs will be normal and CT often will not assist in diagnosis. Post fracture, the medial unicortical beak is characteristic and CT (performed for surgical planning as the fracture would be obvious on radiographs) will only help in further assessing the fracture anatomy.

The appearances tend to be similar to those seen in stress fractures. The typical periosteal callus seen prior to

Figure 7. Female patient (same patient as in Figure 6). Technetium-99m methylene diphosphonate bone scintigram shows uptake in the region of the acute fracture (localised to the cortices). No evidence of metastatic bone disease. Degenerative changes only. Ant, anterior; Post, posterior.

occult stress fracture is evidence of an attempt at repair. Callus formation has been seen on the lateral aspect of the femur prior to atypical femoral fractures, although there is often a more generalised cortical thickening. The evidence for this is again unclear as there is genetic variance in cortical thickness, and there is no evidence to suggest that the processes thought to be responsible for atypical fractures cause enhanced endosteal formation or periosteal apposition.

MRI

MRI of a complete atypical femoral fracture will show a fracture line of low signal intensity on all sequences, traversing an area of bone marrow oedema, represented by diffusely decreased signal intensity on T1W sequences and increased signal intensity on T2W and STIR sequences [32]. A single coronal T1W or STIR sequence may be sufficient and there is no need for iv contrast administration [42]. However, the role of MRI is more important in making the diagnosis before the complete fracture occurs and in this respect it is the most sensitive modality. The findings at this stage are essentially the same as in insufficiency or stress fracture, but characteristically they occur along the lateral aspect of the femur, starting with some periosteal high signal and normal marrow on

Figure 8. Female patient (same patient as in Figure 6). Radiograph taken for intermittent left thigh pain approximately 1 year after previous admission. There is focal thickening of the lateral cortex in the upper femoral diaphysis (asterisk).

STIR, progressing through an increasing amount of periosteal changes and marrow oedema [42]. Cortical thickening may be evident. Doubt may occur as to the nature of the bone oedema, and distinction from a pathological fracture or neoplastic lesion may be needed, aided by the linear nature of the marrow oedema [41] and absence of any well-defined T1W lesion, endosteal scalloping or soft tissue mass [43].

MRI also has an important role in the assessment of the contralateral femur in patients with atypical femoral fracture. Irrespective of whether the contralateral side is symptomatic, following a normal or inconclusive radiograph, MRI should be performed to look for signs of bone oedema [42].

Figure 9. Female patient (same patient as in Figure 6). Readmitted following sudden onset of left thigh pain following minor trauma approximately 6 months after radiograph shown in Figure 8. (a) Transverse diaphyseal fracture through the upper left femur with medial unicortical beaking (straight arrow) and cortical thickening (wavy arrow). (b) Post-operative films demonstrate the lateral cortical thickening and early callus formation.

MRI has a role in guiding the treatment of incomplete atypical femoral fractures in asymptomatic patients. A trial of conservative treatment with reduced activity and limitation of weight bearing is deemed successful if MRI shows resolution of bone oedema [42].

Functional imaging

Nuclear medicine studies, most frequently technetium-99m-labelled methylene diphosphonate bone scintigrams, may be performed before or soon after fracture in an attempt to identify a pathological process. The fracture itself will display high uptake (as all fractures will); however, barring the single “hot spot”, most patients will have a normal study. Pre-fracture studies have been described showing mild uptake in the region of the thickened cortex (Figures 7–9).

Management

Once a fracture has occurred, the immediate concern is for stabilisation and surgical fixation (preferentially with an intramedullary nail). Many of these are suspected to be pathological fractures at presentation, but investigation is unremarkable. Patients often re-present with a contralateral fracture, at which point the diagnosis may become more obvious.

At present it is unclear how to manage patients suspected to be developing an atypical fracture from clinical and radiographic signs. In patients at low risk of osteoporotic fracture (clinically assessed using a tool such as the World Health Organization—Fracture Risk and Assessment Tool) [44], bisphosphonates should be discontinued [45]. Das et al [46] recently published a report outlining one management approach, including investigations (bone mineral density, radiographs of both femurs, serum biochemistry markers) and treatment options (prophylactic surgical fixation, post-operative cessation of bisphosphonates, consideration of recombinant parathyroid hormone and serial fracture

risk assessment). They also suggested radiological follow-up of the contralateral femur, which is a common theme in all of the available literature [47].

The Food and Drug Administration in the USA has reviewed the literature on two occasions, most recently in 2010 [48]. In asymptomatic patients the evidence is insufficient to warrant withdrawal of therapy in those who benefit from the effects of bisphosphonates. This was echoed by the Medicines and Healthcare products Regulatory Agency in 2009 [49] and in the American College of Rheumatology hotline report from 2010 [45].

The idea of a “drug holiday” every 5 years of treatment has been postulated in those at intermediate risk of osteoporotic fracture [32, 46–47]. The National Osteoporosis Foundation published a clinical update in 2008 suggesting that for most patients such an approach did not increase the risk of osteoporotic fracture and “may be advantageous”, although it was clinically reasonable to continue bisphosphonate therapy in those at high risk of fracture [2].

Discussion

Bisphosphonates are a crucial weapon in the clinician’s armoury. Their proven benefits have, over the years, prevented many vertebral, hip and other osteoporotic fractures, and improved quality of life. For instance, it has been estimated that for each atypical femoral fracture caused, at least 30 vertebral and 5 hip fractures will be prevented [50]. However, the described complications are significant, need to be expected and are likely to become more frequently seen as prescription numbers rise.

BRONJ is a well-known skeletal phenomenon associated with bisphosphonate therapy in certain high-risk groups, namely patients receiving high doses of iv bisphosphonates. Problems tend to arise as a result of dental work, which overloads the capacity for bone repair, either prior to or during bisphosphonate therapy.

While this is often detected clinically, radiographic correlation is used to assess evolution and, hopefully, resolution. When bone is not directly exposed it is a challenge to detect, and it is essential that we, as radiologists, be alert to the possibility of osteonecrosis of the jaw and look for the subtle signs.

Whether there is a causal relationship between bisphosphonate therapy and atypical fractures is widely debated, but as yet unresolved, as summarised in the recent position paper produced jointly by the European Society on Clinical and Economic Aspects of Osteoporosis and the Osteoarthritis and International Osteoporosis Foundation [51]. The interesting (and concerning) issue has been that the link is not with high-dose iv bisphosphonate therapy in patients with underlying malignancy (as in BRONJ), but in the general osteoporotic population who are on long-term oral bisphosphonate (alendronic acid) therapy. This encompasses a much larger cohort, and yet although this is a relatively well-known phenomenon within endocrine and ortho-geriatric circles, it appears to have largely bypassed the radiological community.

The typical imaging findings are quite characteristic once a fracture has occurred. During the prodromal phase, many radiographs will be normal; however, a percentage will display a subtle area of cortical thickening, and this could potentially be an area in which we as radiologists can raise awareness in the correct clinical setting.

Clinical radiologists, although not directly managing patients, have the responsibility to ensure that appropriate questions are raised when imaging findings suggest complications of bisphosphonate therapy. We need to be alert to the potentially devastating skeletal complications associated with mandibular osteonecrosis (without history of radiotherapy), or when a low-impact horizontal/short oblique non-comminuted fracture or lateral cortical thickening occur in the femoral diaphysis, especially in a patient with a preceding history of deep thigh or groin pain. Bilateral atypical femoral fractures, either simultaneous or sequential, should definitely trigger suspicion of bisphosphonate therapy complication. In unilateral atypical femoral fractures, imaging of the contralateral femur should be initiated. At present there is lack of awareness and under-reporting of the often subtle skeletal complications of bisphosphonate therapy among radiologists.

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