Acta Orthop. Belg., 2017, **83**, 558-567

ORIGINAL STUDY

Atypical Femoral Fractures: Three cases and a review of literature.

Marno Van Lieshout, Guy Putzeys, Stefan Goemaere, Catherine Van Der Straeten, Emmanuel Audenaert

From AZ Groeninge, Kortrijk, Belgium and Ghent University Hospital, Belgium.

In recent years, bisphosphonates and RANK-ligand inhibitors have become the mainstay of treatment for multiple types of osteoporosis, as well as several other metabolic bone diseases. Although rare, atypical femoral fracture is a recent but clearly defined complication of antiresorptive therapy with bisphosphonates, and likely also with denosumab. In this article, we present 3 different cases of atypical femoral fracture: an incomplete fracture linked to a bisphosphonate, an incomplete fracture linked to denosumab, and a complete atypical femoral fracture. Specific diagnostic steps and therapy are described. We also offer a complete overview of available literature concerning diagnosis, epidemiology, pathogenesis, treatment and future outlooks concerning this entity. Although antiresorptive therapy offers a very significant benefit in the prevention of osteoporotic fractures, clinicians should be aware of the possible complications, especially with long-term therapy.

Keywords : Atypical femoral fracture ; biphosphonates ; RANK-ligand-inhibitors.

INTRODUCTION

Bisphosphonates including oral bisphosphonates (i.e. alendronate, risedronate and ibandronate) and intravenous bisphosphonates (i.e. zolendronate and ibandronate) have become the backbone of the treatment for proven postmenopausal, male and corticoid-induced osteoporosis. Alendronate has demonstrated a clinically relevant benefit in the secondary prevention of all osteoporotic fractures. However, a statistically significant effect with regard to the primary prevention of osteoporotic fractures could not be demonstrated, with the exception of vertebral fractures, for which the decreased incidence was clinically pertinent *(29)* . Risedronate demonstrated an important clinical benefit in the secondary prevention of the majority of osteoporotic fractures. Statistically significant reductions in the number of vertebral, non-vertebral and hip fractures were observed with the exception of fractures of the wrist). There was no statistically significant effect on the primary prevention of vertebral and non-

■ Marno van Lieshout[1], MD, MSc, Resident.
■ Guy Putzeys[2], MD, Orthopaedic and Trauma Surgeon.
■ Stefan Goemaere[3], MD, PhD, Rheumatologist.
■ Catherine Van Der Straeten[4], MD, PhD.
■ Emmanuel Audenaert[5], MD, PhD, Orthopaedic Surgeon.

[1]*Orthopaedic surgery & Traumatology*, *Ghent University Hospital*.
[2]*AZ Groeninge Kortrijk, Belgium.*
[3]*Unit for Osteoporosis and Metabolic Bone Diseases, Ghent University Hospital, Belgium.*
[4]*Imperial College London UK, Faculty of Medicine, Division Surgery and Cancer, Musculoskeletal Sciences and Technology, Department of Physical medicine and orthopaedic surgery, Ghent University Hospital, Belgium.*
[5]*Department of Physical medicine and orthopaedic surgery, Ghent University Hospital, Belgium.*

Correspondence: Marno van Lieshout Weehage 20, 9520 Sint-Lievens-Houtem.

E-mail : marno.vanlieshout@uzgent.be

No benefits or funds were received in support of this study.
The authors report no conflict of interests.

vertebral fractures *(28)*. Bisphosphonates are also considered standard of care for other diseases, e.g. bone metastases *(7)*, Paget's disease*(23),* and may be beneficial for fracture prevention in osteogenesis imperfecta *(27)*.The safety profile of these drugs is acceptable: chemical esophagitis is easily preventable taking into account clear instructions concerning ingestion (such as drinking a large glass of water and remaining upright for thirty minutes after swallowing), whilst the feared osteonecrosis of the jaw is primarily associated with intravenous administration in an oncological setting where a different dosing regimen is used *(2).*

Denosumab, a monoclonal RANK-ligand inhibitor, is a recent addition to the treatment options for osteoporosis with a high fracture risk, and is also used for prevention of pathological fractures. As its mechanism of action is similar to bisphsphonates, osteonecrosis of the jaw is also a feared side effect, with a comparable prevalence*(17)*.

Atypical femoral fractures (AFF) as a side effect of bisphosphonates and denosumab have been reported anecdotally since 2007. Since then, attempts have been made to establish the epidemiology, pathogenesis and treatment of AFF. The diagnostic criteria were first defined in 2010 *(22)* and were updated recently *(21)*. The current evidence suggests that AFFs are stress fractures occurring as a consequence of bisphosphonate impairment of normal bone healing *(21)*. Evidence for an association between bisphosphonate use and AFFs has continued to accumulate and is quite robust *(21)*.

In this article, we present three cases of AFF and offer an overview of the current state of the art regarding pathogenesis, diagnosis and treatment

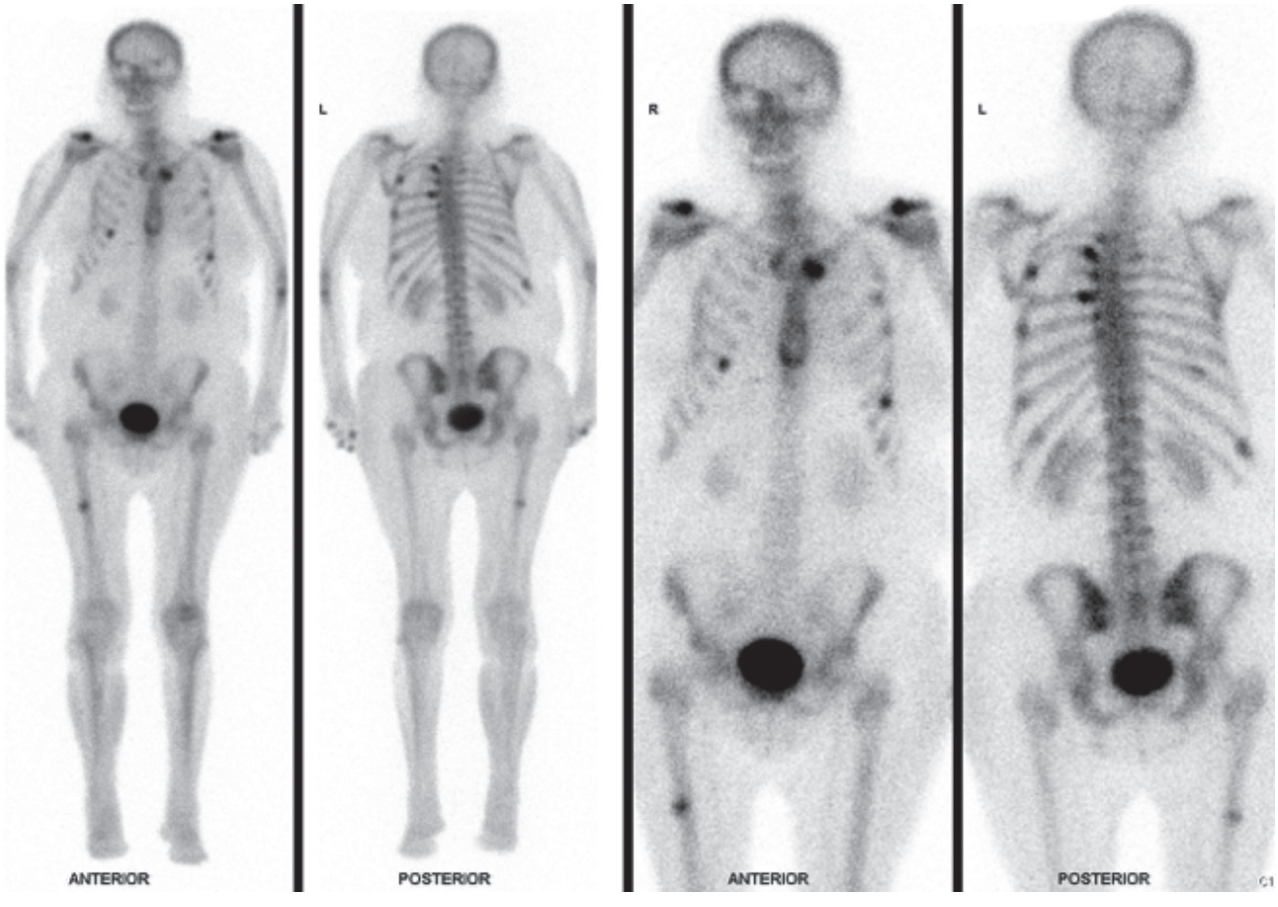

Fig. 1. — Increased focal bone turnover in the lateral cortex of the right femoral shaft. Increased bone turnover of traumatic origin in multiple ribs, multiple costochondral junctions and multiple vertebrae. Degenerative increased activity in hips, acromioclavicular and sternoclavicular joints bilaterally.

of this condition. Literature in English from the past decade was reviewed using atypical femoral fracture, bisphosphonates and denosumab as search terms in major scientific search engines. Additional publications were identified through bibliography of the reviewed papers.

First Case

In 2011, a 58-year-old woman presented at our orthopaedic department complaining of increasing pain in the right thigh. The pain had appeared spontaneously over the course of a few weeks, and wasn't preceded by trauma or unusual exercise. The patient's medical history was extensive: pneumonectomy due to bronchiectasis, corticosteroid-dependent asthma, multiple deep venous thromboses and atrial fibrillation. Relevant medication included longstanding use of 16mg of methylprednisolone per day, risedronate since 1993 for proven osteoporosis, and a daily calcium/vitamin D supplement (1000mg of calcium, 880 IU of vitamin D). Physical examination yielded no specific origin for her pain. Bone scintigraphy (fig 1) showed an ipsilateral midfemoral hotspot (besides other hotspots indicative of degenerative skeletal changes), possibly compatible with a bone metastasis. Standard radiographs however, only revealed a cortical irregularity in the lateral cortex, with a minuscule cortical translucency, extending discretely to the medulla. Two months later, the radiographic findings were more obvious (fig 2). The patient was diagnosed with a stress fracture of the femur and treated by reamed intramedullary nailing with proximal and distal locking in January 2012. Within 4 days, the patient was ambulatory and experiencing noticeably less pain. In mid-2012 an open reduction and cable fixation of a long-standing patellar nonunion after spontaneous fracture was performed; in early 2013 she underwent a vertebroplasty for a fracture of the 12th thoracic vertebra followed by fractures of the 8th thoracic and 4th lumbar vertebrae. Because of these multiple consecutive fractures, antiresorptive therapy was discontinued and substituted by daily injections of teriparatide.

In July of 2013, the patient presented again with marked pain in her right thigh and almost unable to walk. Radiographs still showed a cortical translucency on the lateral side, featuring as a hotspot on bone scintigraphy. It was hypothesized that the intramedullary nail provided insufficient

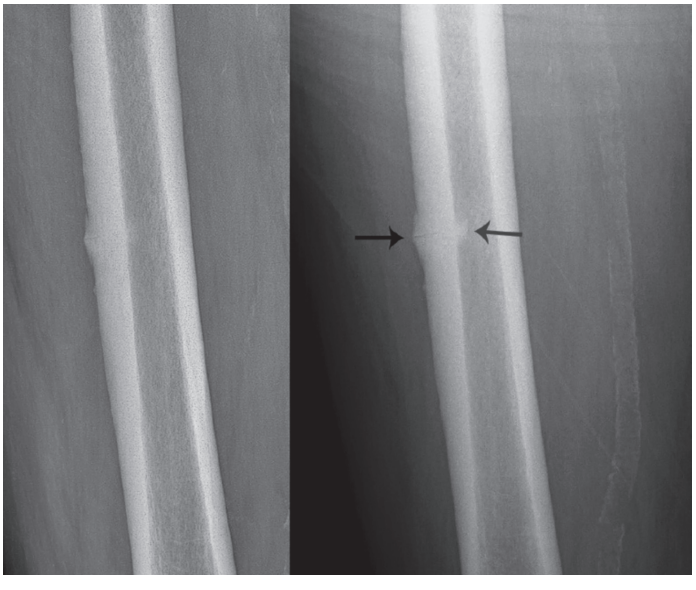

Fig. 2. — Initial radiography (left) and follow-up radiography (right) of the right femur after 2 months. Marked periosteal (black arrow) and endosteal (grey arrow) reaction around a fine transversal cortical translucence originating from a thickened lateral cortex. Severe calcification of the femoral artery.

stability for healing of the non-union and a long, locking, periprosthetic proximal femoral plate was added. In the postoperative course the pain subsided gradually. In April 2014, 1 year after the second surgery, a CT-scan of the femur showed bridging callus and the patient was painfree.

Second Case

A 79-year-old woman presented at our rheumatology department in March 2013, unable to bear weight on her left leg. There was no recent history of fall or any other trauma. The patient's medical history included rheumatoid arthritis, fibromyalgia, osteoporosis with vertebral fractures, lumbar degenerative disc disease, hypertension and Cushing's syndrome secondary to corticosteroid treatment. Because of the high fracture risk, the osteoporosis was being treated with denosumab, of which the patient had already received 2 subcutaneous injections with a six-month interval. Electromyography revealed a marked polyneuropathy; lab results showed a raised CRP of 22 mg/L and reduced vitamin D levels. The tentative diagnosis was sciatica, but epidural injections did not provide pain relief. Therefore a bone scintigraphy was performed, showing a subtrochanteric hotspot in the left femur, besides accentuation of the lumbar vertebrae. Conventional radiography showed a thin cortical translucency, originating from the lateral cortex, with a sharp solid periosteal reaction. Bone densitometry yielded a T-score of -2.1 standard deviations. This stress fracture was prophylactically nailed with proximal and distal locking. The initial postoperative evolution was favourable, with decreased pain and autonomous ambulation on the tenth postoperative day. In June 2013, the patient presented with similar symptoms, on the contralateral right side. Radiographs showed periosteal and endosteal reaction in the subtrochanteric region. On CT-scan revealed a very subtle fracture line was seen at the same level. The fracture was treated with a long proximal femoral nail because of its subtrochanteric location. The pain subsided and the patient could walk again. Follow-up radiographs and CT-scan showed good callus formation, but delayed healing of the fracture (fig 3).The patient reported no symptoms on the right leg anymore but the pain in the left upper leg persisted and progressed. In December 2013 callus formation was demonstrated on CT scan but no bridging of the fracture site. In March 2014 the evolving, disabling pain was attributed to a non-union of the stress fracture of the left femur. In April 2014 a second surgery was performed on the left femur. A locking plate was applied to add stability and autologous bone grafting was performed. During follow-up the patient continued to experience pain in the left leg, presumably caused by the subcutaneous osteosynthesis material. In September 2015 the locking plate was removed. In October 2015 radiographic healing of the fracture was confirmed but the patient still suffered from pain in the left thigh.

Third Case

A 74-year-old woman presented at our outpatient clinic in 2011 with non-traumatic pain in the left thigh. The patient had been diagnosed with osteoporosis in 2000, and treated with raloxifene.

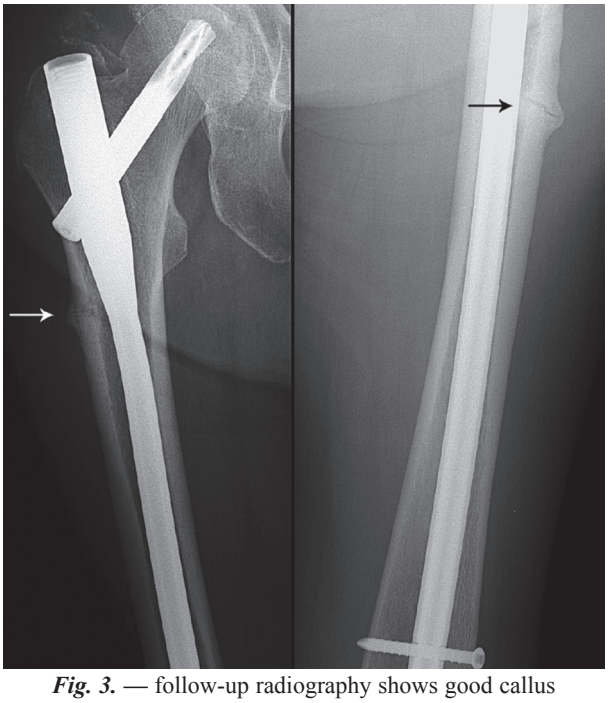

Fig. 3. — follow-up radiography shows good callus formation on both the right (white arrow) and left (black arrow) side, yet with a persistent marked fracture line of the left femoral shaft.

In 2004 a dual-energy x-ray absorptiometry (DXA) scan was performed, which revealed a T-score of -2.9 standard deviations; raloxifene was replaced with daily oral alendronate, a bisphosphonate. In 2009, the patient lost her equilibrium while dressing, fell and fractured her right femoral shaft and left forearm. Plain XRays of her left hip and femur to reassess the persistent non-traumatic pain onlyrevealed a mild coxarthrosis. Treatment was conservative with paracetamol and NSAIDs. In December 2013 she presented at the emergency department with a complete transverse fracture of the left femoral shaft (fig 4) after a sudden and unexplained fall. Upon retrospection the 2011 radiographs already showed a discrete translucency originating at the lateral cortex. This spontaneous femoral fracture, transversely across the bone without communition, and probably related to the translucent line seen on earlier imaging, was categorized as an atypical femoral fracture.

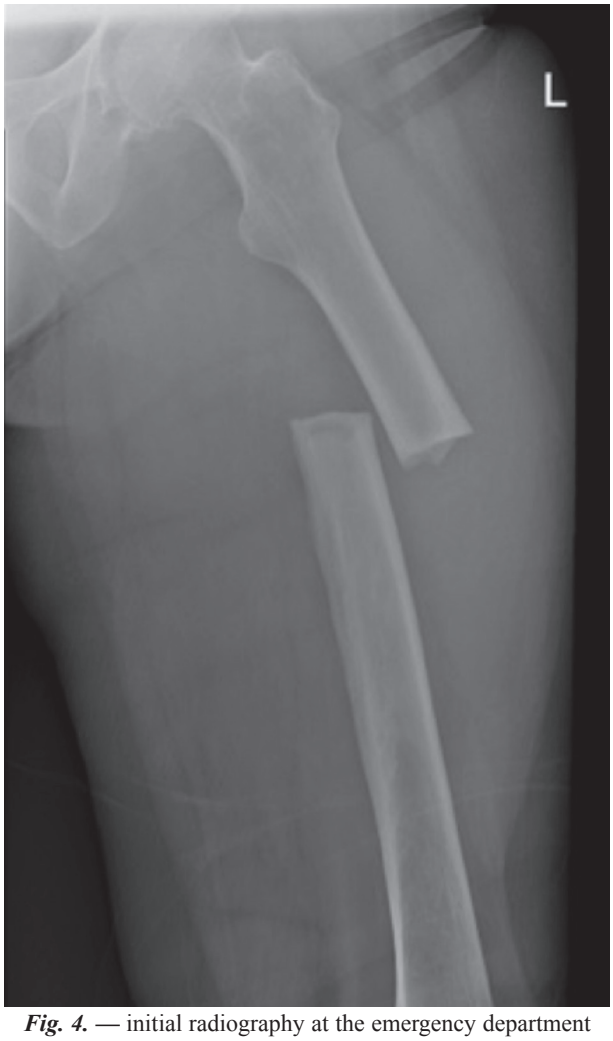

Fig. 4. — initial radiography at the emergency department shows a complete, transverse, non-comminuted fracture of the left femoral shaft, with a medial spike. Due to rotation, periosteal reaction and lateral cortical thickness is difficult to assess on this radiograph.

The fracture was surgically treated with a distally locked, long cephalo-medullary nail. Antiresorptive therapy was immediately stopped. Calcium and vitamin D supplementation was initiated. Follow-up radiography showed correct placement of the hardware and good healing of the fractures. At last follow-up in October 2015 the patient had resumed all preoperative activities and only mentioned sporadic mild pain in the left thigh.

DISCUSSION

AFF was first reported as a possible complication of long-term bisphosphonate use in a 2005 case series by Odvina et al. The authors described AFF as non-traumatic, caused by severe suppression of bone turnover, and linked to corticosteroid use *(16).* Following several case reports and case series, a 26-member task force of the American Society for Bone and Mineral Research first defined the AFF in 2010, and in 2013 revised the definition as: "The fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare". In addition, at least four of five Major Features must be present. None of the Minor Features is required for the diagnosis but are sometimes associated with AFF *(21)*. The major, minor and exclusion criteria are summarised in table 1.

There is currently no scientific consensus regarding the optimal duration of antiresorptive therapy with bisphosphonates. It is advisable to tailor antiresorptive therapy intensity and duration to the individual patient's fracture risk. The FRAX fracture risk tool, developed by the World Health Organisation to evaluate individual 10-year hip fracture and major osteoporotic fracture risk, integrates both clinical risk factors and bone mineral density (BMD) at the femoral neck *(14)*. Multiple authors, such as Diab et al and Ro et al,

Table I. — Major, minor and exclusion criteria for the diagnosis of an atypical femoral fracture. Reproduced from the ASBMR

Major features
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, as in a fall from a standing height or less
Transverse or short oblique configuration
Noncomminuted
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
Minor features
Localized periosteal reaction of the lateral cortex
Generalized 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 (eg, vitamin D deficiency, rheumatoid arthritis, hypophosphatasia)
Use of pharmaceutical agents (eg, BPs, glucocorticoids, proton pump inhibitors)
Excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (eg, Paget's disease, fibrous dysplasia)

have suggested using the individual osteoporotic fracture risk to stratify fracture risk and offer a 'drug holiday' after 5 tot 10 years until there is significant loss of BMD or the patient has a fracture *(5,18)*.

The diagnosis of AFF in our presented cases was made on the basis of the ASBMR criteria described earlier in this article. In all 3 cases, all 5 major features (ASBMR) were present.

Pathogenesis and Epidemiology

Even though the exact pathogenesis of AFF is still unclear, multiple contributing mechanisms have been proposed. AFFs share many properties with stress and insufficiency fractures, but contrary to stress fractures, AFFs originate in the lateral cortex, are more transverse instead of oblique, and are more variable regarding location in the femur. It has been theorized that AFFs are largely due to suppression of normal bone turnover, which leads to the accumulation, and confluence of microcracks under normal loading. Biopsy studies showing normal lamellar bone with largely absent osteoclasts and reduced osteoblastic populations seem to confirm this *(13,15)*. Finally, Saita et al have suggested that lower limb geometry and femoral curvature are correlated with the occurrence of AFFs due to increased biomechanical stress *(19)*. Epidemiological studies on the prevalence of AFFs can roughly be split into two categories: studies where AFFs are identified in large databases using ICD-codes for subtrochanteric and femoral shaft fractures, and linked to national drug prescription databases; and studies where AFFs are established in radiological reviews, preferably using the ASBMR-criteria. A systematic review by Gedmintas et al described the heterogeneity of the available epidemiological studies, and using pooled data calculated an odds ratio of 2.48 (95% CI: 1.53 - 4.01) of developing an AFF while taking bisphosphonates *(9)*. Due to the inclusion of traumatic and pathological fractures in

ICD-based studies without radiological survey, the actual odds ratio is likely to be much higher. This is the case when only radiological review studies are taken into account. Most epidemiological studies, listed and commented in the original ASBMR task force report, suggest an increased fracture risk after 5 years of bisphosphonate use *(22)*. Schilcher et al, used radiological adjudication with ASBMR-criteria in 12777 women 55 years of age or older, and reported the highest absolute risk of AFFs thus far, with 50 cases per 100.000 patient-years (95% CI, 40-70) attributable to bisphosphonate use. The authors also described a 72% reduction in risk for every year after cessation of antiresorptive therapy (multivariable-adjusted OR 0,28, 95% CI 0,21 – 0,38) *(20)*. Girgis et al, among many others, suggested a significant increase of risk with concomitant use of glucocorticoids *(11)*. Although AFFs occur rarely, the increase of bisphosphonate use with the implementation of better osteoporosis management predicts a steep rise of atypical fractures in the future. Until now, only a few case reports have been published describing AFFs in patients receiving denosumab. In our opinion this is related to the fact that denosumab was only FDA-approved since 2010, and is less often used than bisphosphonates. The similar mechanism of action of denosumab and bisphosphonates, by inactivation of osteoclasts, suggests that denosumab may be associated with a similar risk of AFF *(1)*. Drampalos et al described a case analogous to our denosumab-patient, with an AFF occurring after only a handful of doses *(6)*. Villiers et al reported on a 78-year old women who suffered an AFF after 3 injections of denosumab *(26)*. Thompson et al even described the case of a 59-year-old women presenting with bilateral atypical femoral fractures after a single dose of denosumab *(25)*. Even though more studies are needed to definitively establish the link between denosumab use and atypical fractures, AFFs have already been incorporated into the denosumab safety information.

Diagnosis

The diagnosis of AFF is largely based on radiological imaging. However, 70% of patients present with prodromal thigh pain and long-term use of bisphosphonates is certainly a risk factor (22). Cortical thickening on plain x-rays may be an early sign but evidence on progression to AFF is lacking. The ASBMR task force recommends switching to a higher level of imaging when it is noticed. Even with initial negative conventional radiography, a high degree of clinical suspicion should warrant more imaging. As with other stress and insufficiency fractures, magnetic resonance imaging (MRI) is the imaging modality of choice for localizing the fracture as well as distinguishing bone edema. Where MRI isn't available, computer tomography (CT) can be used to show a periosteal and endosteal reaction and a fracture line. Bone scintigraphy remains a good screening tool for atypical skeletal pains, but is less specific than MRI or CT. Scintigraphy however is often more readily available than MRI in clinical practice.

In our first case the diagnosis was made fast. In the primary work-up a bone scintigraphy was performed showing the femoral hotspot. With the second case we had a clinical suspicion of sciatica and the diagnostic work-up was performed with this diagnosis in mind. However, since there was no response to therapy further investigation was performed, including bone scintigraphy which again guided our diagnosis. With a higher grade of clinical suspicion we could have ordered plain x-rays and bone scintigraphy earlier, providing us with a faster diagnosis.

The third case presented with non-traumatic thigh pain 2 years before presenting with a complete femoral fracture. In retrospect the diagnosis could have been made 2 years earlier with the information that was available. A higher grade of clinical suspicion would have drawn more attention to the translucent line in the lateral femoral cortex.

When addressing future cases, more attention should be paid at the careful inspection of conventional x-rays. When in doubt additional scintigraphy, MRI or CT-scan should be performed.

Regardless of the imaging modality that is used, the most important element in the diagnosis of AFF is clinical suspicion. A careful medical history and knowledge about AFF are essential elements.

Treatment

Firstly, antiresorptive therapy should be discontinued in patients with a proven AFF, whether the fracture is complete or incomplete*(22)*. Calcium and vitamin D status should be assessed and corrected as needed.

Medical treatment

Non-operative management may be considered in incomplete fractures. There is only limited or anecdotal evidence concerning medical management of AFF, but teriparatide, a recombinant parathyroid hormone used in severe refractory osteoporosis and as an off-label treatment in cases of non-union, seems promising in promoting fracture healing. Many case reports of successful teriparatide use have been published, but larger studies are lacking *(12,21,24)*. In a prospective study by Chiang et al involving 14 patients with atypical fractures, administration of 20 μg of teriparatide daily for 6 months to 5 of the 14 patients was associated with increased bone remodelling, improved healing of atypical fractures and pain relief. However, the small sample size and lack of randomisation is a limitation of this study *(4)*. Teriparatide has to be administered daily via subcutaneous injection, and its reimbursement is subject to strict regulations.

Surgical treatment.

Treatment for a complete AFF is always surgical *(21)*. The choice between a regular femoral nail and a cephalomedullary nail is based on the location of the fracture, as with other types of fractures. In multiple case series, Egol et al showed total but very delayed healing of complete fractures after nailing, with a median radiological healing time of 8,3 months. Functional results, however, are only moderately sucessful, with only 66% of patients achieving pain-free status and only 64% reporting a return to former functioning *(8)*. Chiang et al. reported non-union after one year in 7 of 9 patients treated with intramedullary nailing *(4)*. Most authors also recommend prophylactic nailing of incomplete fractures *(22)*, especially when accompanied by pain, as they can progress to complete femoral fracture. However, in cases of minimal pain, conservative therapy can be tried with limited weight bearing and frequent radiographic follow-up.

In our first case the patient underwent intramedullary nailing but presented with a non-union more than 2 years after the initial surgery. A lack of stability was presumed to be the cause of the non-union and additional plate fixation was performed. One year after the additional stabilization the fracture was healed. The second case is another clear example of the delayed or non-union that complicates the treatment of AFFs. As proposed by other authors the patient was treated with an intramedullary nail. When she presented with a non-union we treated the non-union by trimming the surgical site and applying a locking plate. Although non-union has been described by multiple authors, we could not find a recommendation regarding surgical treatment. The third case was treated with an intramedullary nail. The patient recovered rapidly with uncomplicated return to normal daily activities.

Adjuvant therapy

Since healing of atypical fractures has proven difficult with delayed healing and lower union rates than 'conventional' fractures, the question arises as to whether adjuncts to surgical therapy can be beneficial. Chiang et al. suggested the use of teriparatide as a first therapeutic option in incomplete fractures and as an adjunct to surgery in complete fractures *(4)*. A clinical trial investigating the effect of teriparatide on healing of pertrochanteric femoral fractures is ongoing *(3)*. Until now there is no scientific evidence to use teriparatide as routine practice in AFFs. The beneficial effects of calcium and vitamin D supplementation in osteoporosis are widely accepted and these supplements should always be prescribed (10).

CONCLUSION

Atypical femoral fracture is a recent but clearly defined complication of antiresorptive therapy with bisphosphonates, and likely also of denosumab. Although antiresorptive therapy offers a very

significant benefit in the prevention of osteoporotic fractures, clinicians should be aware of the possible complications, especially with long-term treatment. Comorbidities and concomitant medication should be carefully examined and risk factors should be mitigated. Although admittedly a rare occurrence, it is our perception that some, if not most, diagnoses of AFF are glossed-over or missed, either by orthopedic surgeons, rheumatologists, or radiologists.

The treatment of AFF's is challenging because of higher rates of delayed and non-union. The current standard of care is intramedullary nailing for complete fractures. For incomplete fractures medical treatment with teriparatide is proposed, but until now there are no clinical trials to support this.

At present, the most effective measure in the treatment of AFF is to enhance awareness among orthopedic surgeons and radiologists. Knowledge about the condition and a higher grade of suspicion can lead to an earlier diagnosis, guiding the treating physician to an appropriate treatment.

REFERENCES

1. **Aspenberg P**. Denosumab and atypical femoral fractures. *Acta Orthop*. 2014 ; 85 : 1–1.
2. **Cartsos VM, Zhu S, Zavras AI**. Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. *J Am Dent Assoc*. 2008 ; 139 : 23–30.
3. **Chesser T, Fox R, Harding K, et al.** The administration of intermittent parathyroid hormone affects functional recovery from pertrochanteric fractured neck of femur: a protocol for a prospective mixed method pilot study with randomisation of treatment allocation and blinded assessment (FRACT). *BMJ Open*. 2014 ; 4 : e004389.
4. **Chiang CY, Zebaze RMD, Ghasem-Zadeh A, Iuliano-Burns S, Hardidge A, Seeman E**. Teriparatide improves bone quality and healing of atypical femoral fractures associated with bisphosphonate therapy. *Bone*. 2013 ; 52 : 360–5.
5. **Diab DL, Watts NB**. Bisphosphonate drug holiday: who, when and how long. *Ther Adv Musculoskelet Dis*. 2013 ; 5 : 107–11.
6. **Drampalos E, Skarpas G, Barbounakis N, Michos I**. Atypical femoral fractures bilaterally in a patient receiving denosumab. *Acta Orthop*. 2014 ; 85 : 3–5.
7. **Early Breast Cancer Trialists' Collaborative Group**. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet*. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Open Access article distributed under the terms of CC BY; 2015 ; 386 : 1353–61.
8. **Egol K a., Park JH, Rosenberg ZS, Peck V, Tejwani NC**. Healing delayed but generally reliable after bisphosphonate-associated complete femur fractures treated with IM nails. *Clin Orthop Relat Res*. 2014 ; 472 : 2728–34.
9. **Gedmintas L, Solomon DH, Kim SC**. Bisphosphonates and risk of subtrochanteric, femoral shaft, and atypical femur fracture: A systematic review and meta-analysis. *J Bone Miner Res*. 2013 ; 28 : 1729–37.
10. **Gehrig L, Lane J, O'Connor MI**. Osteoporosis: management and treatment strategies for orthopaedic surgeons. *J Bone Joint Surg Am*. 2008 ; 90 : 1362–74.
11. **Girgis CM, Sher D, Seibel MJ**. Atypical Femoral Fractures and Bisphosphonate Use. *N Engl J Med*. 2010 ; 362 : 1848–9.
12. **Huang H-T, Kang L, Huang P-J, et al.** Successful teriparatide treatment of atypical fracture after long-term use of alendronate without surgical procedure in a postmenopausal woman: a case report. *Menopause*. 2012 ; 19 : 1360–3.
13. **Jamal S a, Dion N, Ste-Marie L-G**. Atypical femoral fractures and bone turnover. *N Engl J Med*. 2011 ; 365 : 1261–2.
14. **Kanis JA, McCloskey E V., Johansson H, Oden A, Ström O, Borgström F**. Development and use of FRAX® in osteoporosis. *Osteoporos Int*. 2010 ; 21 : 407–13.
15. **McDonald MM, Schindeler A, Little DG**. Bisphosphonate treatment and fracture repair. *BoneKEy-Osteovision*. 2007 ; 4 : 236–51.
16. **Odvina C V., Zerwekh JE, Rao DS, Maalouf N, Gottschalk F a., Pak CYC**. Severely suppressed bone turnover: A potential complication of alendronate therapy. *J Clin Endocrinol Metab*. 2005 ; 90 : 1294–301.
17. **Qi W-X, Tang L-N, He A-N, Yao Y, Shen Z**. Risk of osteonecrosis of the jaw in cancer patients receiving denosumab: a meta-analysis of seven randomized controlled trials. *Int J Clin Oncol*. 2014 ; 19 : 403–10.
18. **Ro C, Cooper O**. Bisphosphonate drug holiday: choosing appropriate candidates. *Curr Osteoporos Rep*. 2013 ; 11 : 45–51.
19. **Saita Y, Ishijima M, Mogami A**. Association between the fracture site and the mechanical axis of lower extremities in patients with atypical femoral fracture. *J Bone Miner Res*. 2012 ; 27 : suppl 1.
20. **Schilcher J, Michaëlsson K, Aspenberg P**. Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med*. 2011 ; 364 : 1728–37.
21. **Shane E, Burr D, Abrahamsen B, et al.** 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.
22. **Shane E, Burr D, Abrahamsen B, et al.** Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American society for bone and mineral research. *J Bone Miner Res*. 2010 ; 25 : 2267–94.

23. Silverman SL. Paget disease of bone: therapeutic options. *J Clin Rheumatol*. 2008 ; 14 : 299–305.

24. Tarazona-Santabalbina FJ, Aguilella-Fernandez L. Bisphosphonate long-term treatment related bilateral subtrochanteric femoral fracture. Can teriparatide be useful? *Aging Clin Exp Res*. 2013 ; 25 : 605–9.

25. Thompson RN, Armstrong CL, Heyburn G. Bilateral atypical femoral fractures in a patient prescribed denosumab - a case report. *Bone*. 2014 ; 61 : 44–7.

26. Villiers J, Clark DW, Jeswani T, Webster S, Hepburn AL. An atraumatic femoral fracture in a patient with rheumatoid arthritis and osteoporosis treated with denosumab. *Case Rep Rheumatol*. 2013 ; 2013 : 249872.

27. Ward LM, Rauch F. Oral bisphosphonates for paediatric osteogenesis imperfecta? *Lancet*. 2013 ; 382 : 1388–9.

28. Wells G., Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women (Review). *Cochrane Database Syst Rev*. 2008.

29. Wells G, Cranney A, Peterson J et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women (Review). *Cochrane Database Syst Rev*. 2011.