

Clinical management and pathogenesis of Atypical Femoral Fractures

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Key points

1. Atypical subtrochanteric fractures have been associated with the use of both bisphosphonates and denosumab.
2. The balance of benefit vs. risk still favours anti-osteoporosis medication to reduce fragility fracture risk. An estimated 137 hip fractures are prevented for each observed AFF in patients treated with bisphosphonates for osteoporosis.
3. Surgical fixation should be designed to facilitate weight bearing on the fractured femur.
4. The contralateral side should always be assessed for pain and radiological signs of involvement.
5. Further work is needed to understand when to recommend prophylactic nailing and whether to start osteoporosis therapies to prevention fragility fracture at other sites.

Atypical femoral fractures (AFF) are defined as atraumatic or low-trauma fractures located in the sub-trochanteric region or femoral shaft and with characteristic clinical and radiological features[1]. The use of bisphosphonates and denosumab, both anti-resorptives, is associated with a higher risk of AFF; this is unexpected as these therapies significantly reduce the risk of other fragility fractures.

The exact pathogenesis of AFFs is not known and a number of mechanisms are probably involved. AFFs can occur without bisphosphonate exposure, e.g. in patients with hypophosphatasia, pycnodysostosis, osteopetrosis, osteoporosis pseudoglioma syndrome and osteogenesis imperfecta. Hence, some patients with AFF may have underlying bone disorders not yet characterized.

Micro-indentation studies demonstrate that even though patients with AFF have been typically long durations of bisphosphonate use, their indentation characteristics are more similar to untreated fracture patients[2]. More studies are now highlighting geometric differences in the lower limb[3-5] in those who go onto to have an AFF suggesting mechanisms involving bone growth/ adaptation to loading.

The absolute risk of AFF is low and the benefits of therapy for osteoporosis considerably outweigh the risks, preventing 137 hip fracture for every AFF they are associated with[6]. However, the risk of AFF is mainly drawn from observational data and how low adherence to oral bisphosphonates in the wider community has reduced the potential incidence of AFF is unknown.

The clinical management is divided into three broad areas:

- 1) Recovery of fractured side.
- 2) Reduction of AFF risk on the contralateral side.
- 3) Reduction of fragility fracture at other sites.

Key to this pathway is identification of that the patient has had an AFF by the treating clinical team. The 2013 ASBMR guidelines on the epidemiology, pathogenesis and medical management of atypical fractures [7] updated the 2010 guidance. They require at least 4 'major features' of AFF to make this diagnosis:

1. Fracture as a result of a trauma equivalent to a fall from standing height or less
2. The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur
3. Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
4. The fractures are non-communited or minimally comminuted
Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")

Periprosthetic fractures, fractures involving primary or secondary bone tumours are excluded.

The successful recognition of AFF requires increased awareness in all members of the trauma team including orthopaedics, care of the elderly, radiology and specialist nurses. Awareness of this issue needs to be incorporated into the national training learning objectives of each of these specialties. A practical step towards increased awareness would be for the referring team to record the use of anti-resorptive medication in radiology requests for subtrochanteric femoral fragility fractures to alert the reporting radiology team.

Another important consideration is a consistent message to the patient and their family. The patient and family are likely to be unaware how a medication they took pains to take properly in order to reduce fracture risk can increase the risk of AFF. In addition, clinical teams in both primary and secondary care may have missed the importance of prodromal symptoms. This has to be handled sensitively with timely and clear communication across all involved to ensure the patient receives a consistent transparent message.

There have been Department of Health drug safety updates in 2011 for bisphosphonates (<https://www.gov.uk/drug-safety-update/bisphosphonates-atypical-femoral-fractures>) and 2013 for denosumab (<https://www.gov.uk/drug-safety-update/denosumab-60-mg-prolia>), these were designed for physicians. While there is an excellent guide of 12 questions for patients with hip fracture[8], there is a lack of materials for the patient who has had an AFF.

There is ALSO little trial evidence to inform clinical management and decision making for the patient with AFF. However, pathways based upon basic principles

have been developed to harmonize care, and have been implemented in some areas of the country (<http://www.ndorms.ox.ac.uk/friscy.php>)).

Management of the fractured side

The femur of patients with AFF is typically brittle with a thick cortex. Intramedullary nailing is the mainstay of treatment. The key orthopaedic principles include: considered reaming in often narrow femoral canals, optimal nail length to reduce the risk of peri-implant fracture and careful selection of entry point to avoid further varus at the fracture site., Choosing a more medial entry point for the nail creates a valgus force on the fracture site. Whilst the normal objective in fracture surgery is to restore the pre-injury morphology, in AFF it was from that pre-existing position the bone had failed. Therefore, it would be logical to seek and correct pre-existing varus deformity. The fixation should generally incorporate the femoral neck[9]. The aim of surgery is to enable the patient to be weight bearing as soon as possible after surgery

This is particularly important in AFF in order to reduce the load on the contralateral side which is also at risk. A characteristic feature of AFF is delayed healing with fractures sometimes taking over 6 months to unite, leading to ongoing pain and concern for patients and their clinicians[10, 11]. It is important to optimize other potential contributors to poor bone healing, ensuring: 25OH vitamin D > 50 nmol/L, intake of calcium of 700 to 1000mg per day, smoking cessation, taking less than 3 units of alcohol per day, improved control of co-morbidities (inflammatory diseases, diabetes) and an adequate body mass index. While there was initial enthusiasm for using teriparatide for treating AFF with improving bone healing[12] and also reducing contra-lateral risk of AFF, recent observational studies have questioned its efficacy[13] and a number of clinical trials are now underway.

Management of the contra-lateral side or incomplete AFF.

A key aim is to reduce the risk of AFF on the contra-lateral side. In the emergency setting of an AFF, the assessment of the contralateral side can be neglected. Patients with AFF should always be asked specifically about symptoms in the groin or leg on the other side and a baseline radiograph of the contralateral femur should be taken to include the region from the lesser trochanter to the distal supra-condylar flare. Clinicians should be aware that pain is not always present, even in patients with an incomplete fracture.

Cross-sectional imaging of the contralateral leg should not delay treatment of the index fracture. However, all patients with symptoms or suspicion on plain radiographs should have a coronal T1 and FSTIR MR of the unfractured side at the earliest appropriate time. If bone marrow oedema is present, then patients should have protected weight-bearing, as described below, for three months in the first instance and preferably until the MR shows no bone oedema. If MR is not possible, CT should be used to detect a cortical lucency and new bone formation or nuclear bone scanning looking for local areas of high uptake.

To reduce the risk of AFF the key step is to stop the anti-resorptive agent. This highlights the importance of making the diagnosis of AFF, as the usual clinical response for patients suffering a fracture while on treatment is to increase the potency of bone therapy[14]. From epidemiological studies, the risk of AFF is reduced by 70% within 12 months of stopping oral bisphosphonates[15]. It is important to discuss the risk of contralateral fracture with the patient during the acute admission as the patient remains at higher risk of AFF for at least 12 months. As discussed above, the evidence for using teriparatide or other agents to reduce contra-lateral AFF is unclear and we await the results of the current RCTs.

There is a significant mechanical component to the aetiology of AFF[16] and one objective is to reduce the load of this contra-lateral side. Hence, patients with symptoms or MR changes should be encouraged to use a walking aid on the side of the index fracture to reduce the load on the contralateral femur. This contrasts with the usual rehabilitation recommendations after limb surgery where the fractured limb is the one that is protected.

Given the majority of AFF occur whilst the patient is being managed for their osteoporosis in the community, GPs also need to be aware of the key aspects of care. Hence, referrals and consultations from primary care may include those patients with potential incomplete atypical femoral fractures. Key aspects to consider include

- 1) AFF is very unlikely to affect many patients in your practice.
- 2) Salient features include:
 - a. Taking any type of bisphosphonate for at least a year and active treatment within the last 12 months.
 - b. The pain is felt typically in the anterior thigh or groin and is dull or aching in nature.
 - c. Other causes excluded are osteoarthritis from the spine, hip or knee.
- 3) If there is a suspicion of an atypical fracture, consider stopping the bisphosphonate and request an urgent AP + lateral of xray of the whole femur
- 4) If radiograph reports an insufficiency fracture or localized periosteal reaction, consider urgent assessment and make the patient non-weight bearing with a crutch on opposite side to the painful thigh.

The role of prophylactic nailing

The ASBMR 2013 recommend prophylactic nailing in patients with cortical lucency or those with on-going pain despite 2 months of conservative therapy. However, this procedure is not without risk of significant morbidity and potential mortality and therefore requires careful case-by-case discussion between orthopaedic surgeon, physician and patient. Often a 'watch and wait' policy is used, alerting the patient of the importance of reporting symptoms of pain or discomfort on the contra-lateral side. This often increases anxiety in many patients and while unavoidable should be explicitly discussed with the patient and their family as part of their management plan. A watch and wait policy can only work if the patient is provided easy and timely

access to expert assessment and repeat MR imaging. The Fracture Liaison Service may facilitate this.

Management of generalized fragility fracture risk

The management of a patient with AFF requires a re-assessment of their fragility fracture risk. This includes a history of bone and falls risk factors, physical examination for secondary causes of osteoporosis and spine fractures, and selected investigations including blood, urine and DXA techniques to rule out secondary causes and guide treatment.

Recently, there has been a shift in the aim of osteoporosis treatment away from the prevention of low bone density towards the specific prevention of fracture. It is likely that there is a subset of patients who were appropriately commenced on lifelong therapy decades ago but, in light of current knowledge, would no longer thought to be of sufficiency risk to warrant pharmacological treatment.

In those patients thought to still be at high enough risk to warrant pharmacological therapy for bone health, the options are limited. Use of strontium ranelate or teriparatide are not thought to increase the risk of AFF. However, recent MHRA warnings have limited the range of patients who can have strontium and, in the UK, NICE TA 161 thresholds often lead to the need for 'individual funding requests' for teriparatide via the Clinical Commissioning Group, with mixed results. Even if teriparatide is approved, it is not clear what to do after 24 months of treatment, as most centres usually then switch to a potent anti-resorptive therapy with the aim of maintaining the skeletal benefits in patients without an AFF. Another option is to use raloxifene or hormone therapies, but both have their own list of restrictions and risks. There are three options:

- a) Prophylactic nailing of the contra-lateral side accepting the associated surgical morbidity and mortality and then starting anti-resorptive therapy.
- b) Introduction of anti-resorptive with close monitoring for features of AFF. The choice of anti-resorptive is influenced by the ease of stopping the biological action of the anti-resorptive therapy should features of AFF develop.
- c) Keep patient off anti-osteoporosis treatment with aim of reviewing if / when further re-fractures occur or repeating the DXA scan every 2 -3 years. Hence balancing the impact of fragility fracture vs. AFF. However, while the risk of fragility fracture can be estimated, the risk of AFF is unknown but thought to be high if re-exposed to anti-resorptive. This is a significant limitation of the shared decision-making process.

Summary

Overall, therapy with anti-osteoporosis medication is generally safe and AFF are rare. Management of the patient with AFF is complex and involves multiple

disciplines with experience with AFF. There is little strong evidence to inform clinical decisions at an individual patient level but this article highlights key principles for the management of both the AFF and, importantly, the contralateral limb. National and international guidelines would help to standardise care and act as a model against which to test new interventions and pathways.

Acknowledgement

We would like to acknowledge the contribution of the members of FRiSCy including the patients with AFF and their families.

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