

## Commentary

### Long term bisphosphonate therapy & atypical femoral fractures: A word of caution

Osteoporosis is characterized by reduced bone mass with increased bone fragility and increased risk of fractures. It is a common endocrine disorder in India and a major public health problem in the elderly due to the morbidity caused by the fractures. Estimates suggest that more than 25 million people in India have osteoporosis<sup>1</sup>.

Bisphosphonates (BPs) are the most commonly used drugs for the treatment and prevention of osteoporosis, with a well documented favourable safety profile. The commonly used BPs in India include oral alendronate, risedronate, ibandronate and intravenous zoledronate. BPs reduce bone loss by inhibiting osteoclast induced bone resorption, improve the bone density and prevent osteoporotic fractures of the spine and hip. The common side effects of BPs reported are reflux oesophagitis, osteonecrosis of the jaw, transient renal dysfunction, hypocalcemia and acute phase reaction (fever, myalgia and bone pain)<sup>2</sup>.

BPs are widely used to prevent “typical” osteoporotic fractures of the vertebrae and hip (femoral neck and inter-trochanteric region), with clearly proven efficacy<sup>2</sup>. The term “typical” fracture refers to classical osteoporotic fractures and usually occurs in classical sites like spine, femur or wrist. The sites for typical osteoporotic fracture in the femur are the femoral neck and the inter-trochanteric region, which are the most susceptible sites<sup>3</sup>.

Recently, there have been concerns over atypical femoral fractures (AFFs) associated with long-term BP use for osteoporosis<sup>3-11</sup>. It is surprising and paradoxical that these drugs (BPs), which are used to increase bone density and prevent fractures, can cause fractures by themselves. It is important to distinguish these “atypical” fractures associated with BPs, from the “typical” osteoporotic fractures, prevented by the

BPs. Atypical fracture refers to stress/fragility fracture (atraumatic or low-trauma), and has characteristic location, clinical and radiologic features. Atypical fractures occur at unusual sites like femoral shaft or subtrochanteric regions, which have high bone density, are usually very strong and do not usually fracture. Postulated mechanism for AFFs is that BPs accumulate in bone for long duration and cause long-term suppressed bone turnover, which leads to reduced new bone formation and remodelling. This leads to accumulation of dense brittle hypermineralized bone with microcracks and of poor quality, which is fragile and susceptible to fractures<sup>3</sup>.

The association of AFFs with long-term BP therapy has been reported in many case reports and case series<sup>3-11</sup>, and has now become a well-recognized clinical entity. The American Society of Bone Mineral Research (ASBMR) has issued clear diagnostic criteria for the diagnosis of these AFFs<sup>3</sup>. To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the trochanter to just proximal to the supracondylar flare, usually in the proximal 1/3<sup>rd</sup> of the femoral shaft. In addition, at least four of the five major features must be present, which include (i) The fracture is associated with minimal or no trauma, as in a fall from a standing height or less; (ii) 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; (iii) Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve lateral cortex; (iv) The fracture is noncomminuted or minimally comminuted; and (v) Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (beaking or flaring).

None of the minor features is required for the diagnosis, but have sometimes been associated with these fractures. Minor features include generalized increase in cortical thickness of the femoral diaphyses; unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh; bilateral incomplete or complete femoral diaphysis fractures; and delayed fracture healing.

Exclusion criteria for these AFFs are typical osteoporotic fractures (femoral neck or intertrochanteric fractures with spiral subtrochanteric extension), periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumours and miscellaneous bone diseases (*e.g.* Paget's disease, fibrous dysplasia).

In the current issue, Bhadada *et al*<sup>12</sup> have reported a retrospective case series of eight cases of AFFs on long term BP therapy from India and studied their predictors. This is perhaps the first case series from India, with only a few case reports published before<sup>13</sup>. Six patients were on oral alendronate and two were on intravenous zoledronate. Bone mineral density showed osteoporosis in two patients and osteopenia in six patients. The AFFs occurred after a mean duration of 4.5 yr of BP use (range 2-6 yr). Three patients had bilateral AFFs, which is well recognized with this entity. Majority of cases needed surgery with intramedullary nailing. One case was treated with teriparatide injections. Prodrome of pain, cortical beaking and thickened cortices were the major predictors of the AFFs in this study<sup>12</sup>. Prodrome of dull aching pain at the fracture site prior to the occurrence of fracture was almost universal, present in seven of the eight cases. The authors have reported an association with steroid therapy in two cases, as has been reported before, but no association with proton pump inhibitors, which has been reported in prior studies<sup>6</sup>. The authors also highlighted the fact that BP was used even in cases with a normal bone density, indicating misappropriate use of these drugs, which can be avoided.

The limitations of the study was a small sample size (8 patients only)<sup>12</sup>. But, AFFs are rare and hence it is difficult to enrol a large number of patients. Another limitation of the study was that bone turnover markers and histomorphometry were not studied in these cases and hence pathogenic mechanisms could not be studied in detail. There was no control group for comparison also, which made evaluation of causal link impossible.

Many case series confirmed the association of BPs with AFFs<sup>3-11</sup>, which is in line with the results

published by Bhadada *et al*<sup>12</sup>. However, there are other large studies, which negate this association and report that AFFs are not more common in patients on BPs, as compared to the general population, suggesting that AFFs also are due to osteoporosis<sup>14,15</sup>.

What are the practical implications of this study to our clinical practice? This study highlights the fact that long-term BP therapy is associated with AFFs. But, it is important to understand that this is only an association, and a clear causal link has not been established yet. This means that AFFs can also occur in people not on BPs, but are more frequent on those on BPs (relative risk is high). Overall, the absolute risk for AFFs on BPs is very low. These AFFs are quite rare even on long-term BP therapy (estimated < 1 AFF for 1,000 patient-years of BP use)<sup>3,14</sup>. Hence, the occurrence of these AFFs during long-term BP therapy should not give a wrong message that we should panic and stop using BPs completely. BPs have been in clinical practice for many years, and the number of osteoporotic fractures prevented (estimated 33 osteoporotic vertebral and non-vertebral fractures prevented per 1000 patient-years of BP use) clearly outweighs the number of uncommon AFFs (estimated < 1 per 1,000 patient-years of BP use)<sup>3,14</sup>. However, physicians need to be aware of these atypical fractures and review the decision to continue BPs for duration of more than five years. Drug holidays for BPs after five years of use depending on the clinical circumstances (if low risk of fracture) would be useful to prevent AFFs. Indications for BP use have to be clearly decided, so that the risk-benefit ratio is clearly favourable. Inappropriate use of BPs should be avoided.

Various international societies including ASBMR and Endocrine Society recommend that physicians prescribing BPs should be aware of these potential AFFs associated with long-term BP use. At present, evidence suggests that AFFs are very rare in patients on long-term BP therapy. Since patients taking BPs have osteoporosis and are at high risk for typical osteoporotic fractures, patients and their health providers must weigh the risk-benefit ratio of ongoing therapy with BPs. The benefits of BP therapy, with clearly proven efficacy in fracture risk reduction in osteoporotic patients, still clearly outweighs the risk of these rare AFFs. Nevertheless, it is recommended that physicians remain vigilant in assessing their patients treated with BPs for osteoporosis. Patients with pain in the hips, thighs or femur should be radiologically assessed and, where a stress fracture is evident, the physician should decide whether BP therapy should be discontinued

pending a full evaluation, based on an individual risk-benefit assessment. The radiographic changes should be evaluated for orthopaedic intervention, since surgery prior to fracture completion might be advantageous, or be closely monitored<sup>3,16,17</sup>.

Management of these AFFs includes discontinuation of BPs and adequate calcium and vitamin D supplementation. Surgery with intramedullary reconstruction full length nailing is recommended for all complete AFFs. Prophylactic reconstruction with nail fixation is recommended for incomplete fractures (with cortical lucency) accompanied by pain. Teriparatide injections should be considered for cases which appear not to heal 4-6 weeks after surgical intervention<sup>3</sup>.

To conclude, the study by Bhadada *et al*<sup>12</sup>, highlights the fact that clinicians should be aware of the entity of AFFs and their association with long-term BP use. This does not mean that we should stop using BPs completely. The occurrence of these AFFs is very rare as compared to the number of fractures prevented by BPs. Hence, the risk-benefit ratio is clearly in favour of BP use. However, high index of suspicion is needed for diagnosing AFFs while on long-term BPs. Patients on long-term BPs with spontaneous or traumatic thigh or groin pain should undergo radiograph of the hip. Patients with AFFs on one side must undergo radiograph on the opposite side, as bilaterality is common. BPs should be used judiciously and drug holidays should be considered for patients on long-term BPs, with low risk of osteoporotic fracture.

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