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ORIGINAL STUDY

Subtrochanteric stress fractures in patients on oral bisphosphonate therapy : an emerging problem

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The emergence of a new variant of subtrochanteric stress fractures of the femur, affecting patients on oral bisphosphonate therapy, has only recently been described. This fracture is often preceded by pain and distinctive radiographic changes (lateral cortical thickening), and associated with a characteristic fracture pattern (transverse fracture line and medial cortical spike). A retrospective review (2007-2009) was carried out for patients who were taking oral bisphosphonates and who sustained a subtrochanteric fracture after a low velocity injury. Eleven fractures were found in 10 patients matching the inclusion criteria outlined. All were females, and taking bisphosphonates for a mean of 4.3 years. Five of the 10 patients mentioned prodromal symptoms, for an average of 9.4 months before the fracture. Although all fractures were deemed low velocity, 5 of 11 were even atraumatic. Two patients had previously sustained contralateral subtrochanteric fractures. Plain radiographs of two patients showed lateral cortical thickening on the contralateral unfractured femur ; the bisphosphonate therapy was stopped and close surveillance was started. Patients taking oral bisphosphonates may be at risk of a new variant of stress fracture of the proximal femur. Awareness of the symptoms is the key to ensure that appropriate investigations are undertaken.

Keywords : oral bisphosphonates ; hip fracture ; subtrochanteric fracture ; osteoporosis.

INTRODUCTION

Oral bisphosphonates are widely used in the treatment of osteoporosis, and work as potent inhibitors of bone resorption. Several randomised clinical trials have shown that bisphosphonates significantly increase bone density and reduce the incidence of fractures in osteoporotic patients (*2,8,15*).

However, a number of recent publications link subtrochanteric fractures with anti-resorptive therapies, predominantly alendronate (*4,6,7,11,12,14,16*). The first series of subtrochanteric insufficiency fractures was described by Goh *et al* (*4*), in 2007, in 9 women taking alendronate. These were associated

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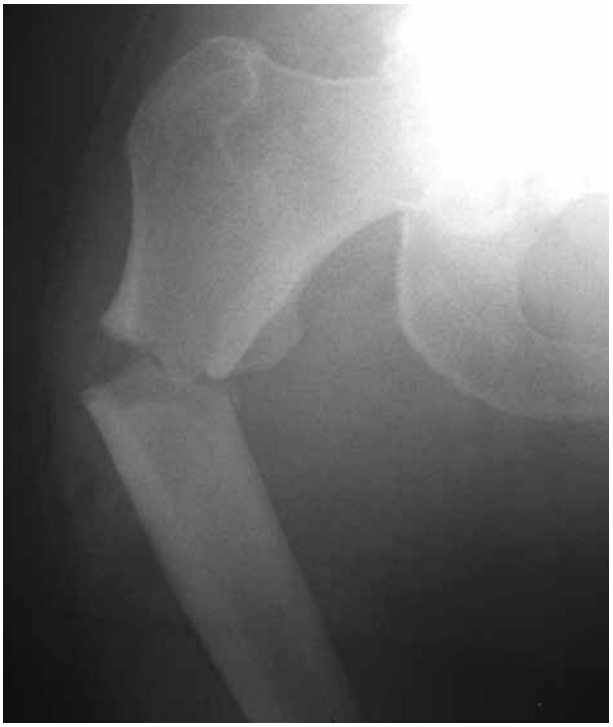

Fig. 1. — Right subtrochanteric fracture with typical radiographic features : lateral cortical thickening and a transverse fracture line.

with prodromal symptoms and distinctive radiographic precursors. A characteristic pattern was described by Kwek *et al* (5), a year later in a series of 17 patients, who featured lateral cortical thickening, a transverse fracture line and a medial cortical spike. The authors, concerned by similar cases (Fig. 1), undertook a review of this cohort of patients.

PATIENTS AND METHODS

All patients with low energy subtrochanteric fractures while taking oral bisphosphonates, admitted to the institution over a two year period (Jan 2007-Dec 2009), were retrospectively studied. Subtrochanteric fracture was defined as a fracture occurring within the femur from the level of the lesser trochanter to the junction of the proximal and middle thirds of the femur. Further data were obtained from the patients via telephone interview, outpatient appointment or family doctor where necessary. Clinical data and radiographs were reviewed. Patients with a high velocity injury or with a possible pathological component were excluded. Radiographs were classified according to the AO/OTA classification system (type A : simple transverse or short oblique ; type B : comminution with medial or lateral wedge ; type C : severe comminution with segmental discontinuity). All subtrochanteric fractures were treated with an intramedullary nail, all intertrochanteric fractures with a dynamic hip screw.

RESULTS

Eleven fractures were found in 10 patients meeting the criteria outlined above, and their details are outlined in Table I. All were female, the average age was 77 years (range 62-97 years), and all were taking oral bisphosphonates on admission. The agents involved were alendronate (8 patients), risendronate (1 patient) and ibandronate (1 patient). The exact duration of the use of bisphosphonates was known for 7 of 10 patients, with a mean of 4.3 years (range 1.5-8 years). An exact figure of how long the other 3 patients were taking oral bisphosphonates was not possible to obtain, with no consensus between patient, previous records, or family doctor.

The injuries were low velocity in all patients (fall from standing height or less), but 5 of the 11 fractures were even atraumatic, occurring during normal daily activities (walking, standing, sitting (Table II). Ten fractures were classified as AO/OTA type A, and one as Type B.

In relation to prodromal symptoms, lateral thigh pain was reported prior to fracture by 5 patients, with a mean duration of 9.4 months (range 1-24 months). Two of the five had investigations for this pain in other institutions ; the first patient received an intra-articular hip injection two weeks prior to fracture (Fig. 2), the second patient had a radiograph of the proximal femur three months prior to fracture deemed normal, but which on review demonstrated evidence of lateral cortical thickening at the level of the subsequent fracture (Fig. 3). The other three patients who reported prodromal symptoms on admission following this fracture did not have any early investigations for their complaints. Unfortunately the notes failed to specify these complaints.

Table I. — Demographics

Patient	Age (years)	Gender	Side of subtroch. fracture	Bisphosphonate agent & duration of treatment (years)	Prodromal symptoms, duration (months)	Previous fractures	Proximal femur status at final follow-up
1	97	Female	Left	Alendronate, 6	No	Right intertroch	Bilateral (IMN, DHS)
2	67	Female	Right	Alendronate, 3	Yes - 12	Bilat DR	Left radiographic changes 4/12 postop – asymptomatic, right IMN
3	62	Female	Left	Alendronate, –	No		Left IMN, right : normal XR 5/12 postop.
4	67	Female	Left	Alendronate, 1.5	Yes - 4	Right subtroch	Bilateral (IMN, IMN)
5	83	Female	Left	Ibandronate, 2	No	Right subtroch DR	Bilateral (IMN, IMN)
6	67	Female	Left	Alendronate, 7	No	DR	Left IMN, right normal XR 14/12 postop.
7	76	Female	Left Right	Alendronate, –	Yes - 1 Yes - 6	DR	Bilateral IMN
8	95	Female	Right	Risendronate, 3	No	Humerus, DR, Left intertroch	Bilateral (DHS, IMN)
9	85	Female	Right	Alendronate, 8	No	TL-Vertebrae	Left Normal XR 2 months postop, right IMN
10	70	Female	Right	Alendronate, –	Yes - 24	DR x2	Left radiographic changes – asymptomatic 10/12 postop, right IMN

DR : distal radius / intertroch : intertrochanteric fracture / subtroch : subtrochanteric fracture / TL vertebrae : thoraco-lumbar vertebrae / IMN : intramedullary nail / DHS : dynamic hip screw / XR : plain radiographs.

Table II. — Type of injury

Slip in kitchen
Gave way walking *
Sitting on bed *
Sitting on sofa *
Slip in bathroom
Fall in kitchen
Slip on carpet
Fall at home
Slip in bathroom
Rising from chair *
Rising from chair *

*atraumatic.

Three patients had bilateral subtrochanteric fractures (Table I) : in one patient (case 7) both occurred during the study period 2007-2009, and in two other patients (cases 4 and 5) one fracture occurred previously to the study period.

Two patients (cases 1 and 8) with a unilateral subtrochanteric fracture had contralateral intertrochanteric fractures, sustained before the study period.

The remaining 5 patients (cases 2, 3, 6, 9, 10) had unilateral subtrochanteric fractures and untreated contralateral femurs. Three of these untreated femurs were roentgenographically normal at 2, 5 and 14 months after the contralateral fracture (cases 3, 6, 9), but the remaining two untreated femurs (cases 2 and 10) had the characteristic radiographic changes ; the bisphosphonate therapy was discontinued, although both patients were asymptomatic.

DISCUSSION

Although oral bisphosphonates have an excellent safety profile, they carry the potential risk of oversuppressing bone turnover, and potentially impairing some of the biomechanical properties of bone.

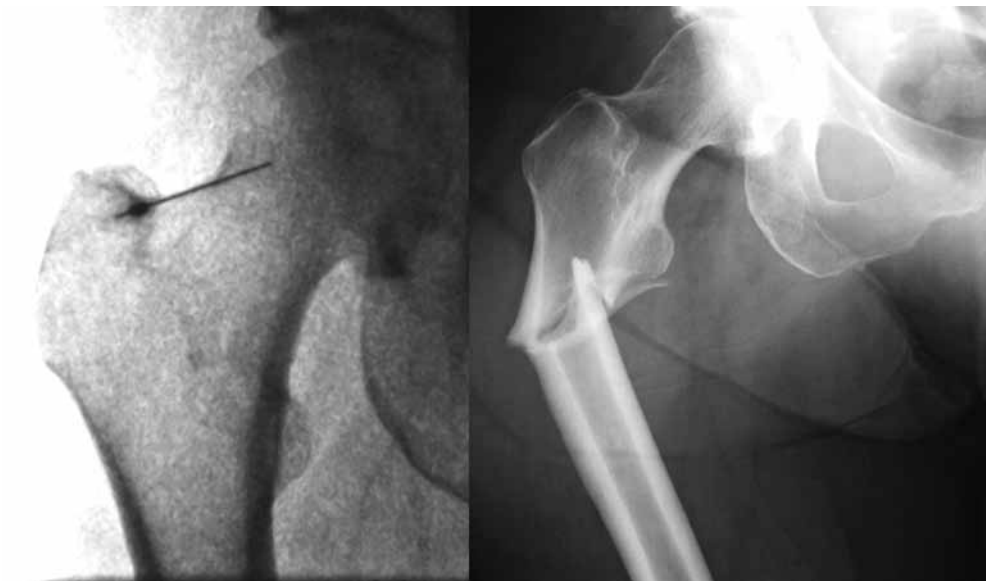

Fig. 2. — This patient had a hip injection for right thigh pain, 2 weeks prior to re-presentation with a fracture through an area with marked lateral cortical thickening. Appropriate imaging of the femur at the time would have demonstrated this.

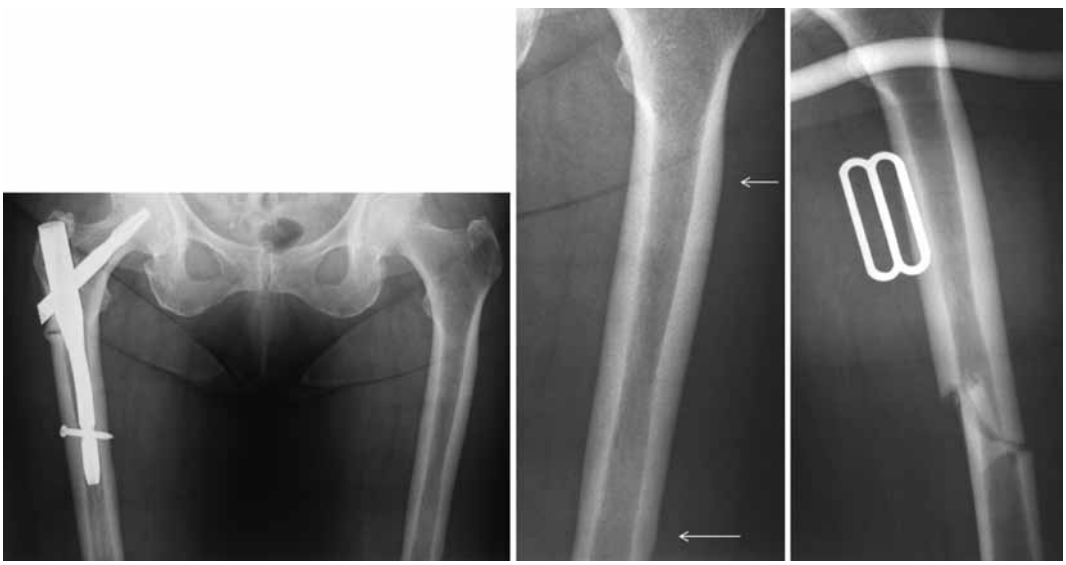

Fig. 3. — Patient investigated for left thigh pain. Despite receiving appropriate imaging, the lateral cortical thickening marked with the arrows (middle) was missed, and the patient subsequently fractured at this site 2 months later (right).

Mashiba *et al* (*9,10*) demonstrated in canine models that alendronate, the most commonly used oral bisphosphonate, inhibits normal repair of microdamage, because of marked suppression of bone turnover, which, in turn, results in accumulation of microdamage. Odvina *et al* (*12*) first reported a case series of spontaneous non-spinal fractures in patients on alendronate therapy. Histomorphometric analysis of bone biopsy samples revealed a marked suppression of bone turnover, with reduced or absent osteoblastic surface in most patients.

The issue of prodromal complaints is interesting. Of the five patients in our series who had prodromal complaints, the two who had their complaints

followed up received either inappropriate or inadequate investigations. For the other three patients a dichotomy exists between the claims of the patients and the lack of documentation of any complaint prior to fracture. This may be due to patient factors – insufficient weighting of the complaint by the patient when communicating with doctors, or doctor factors –, poor communication between the family doctor and hospital doctors, or a lack of awareness of this particular problem causing inadequate or incomplete investigation.

The current series would suggest that surveillance of patients on bisphosphonates, who have sustained a subtrochanteric fracture, is important. Of the 10 patients, 5 now have had bilateral proximal femoral fractures. As to the contralateral femurs of the 5 remaining patients, 3 have had normal radiographs at their last review (at 2, 5 and 14 months post- operatively) and remain on oral bisphosphonates. Two of these 5 patients have radiographic evidence of lateral cortical thickening and 'blebs' on the contralateral femur (at 4 and 10 months postoperatively respectively) although both are currently asymptomatic. Close review of these patients' symptoms and radiographs is warranted. Their medication was stopped.

Recently, the association between such fractures and bisphosphonates has been questioned. These fractures have been suggested to be merely an uncommon subtype of osteoporotic femur fracture (*1*) or a manifestation of a rare metabolic bone disease – adult hypophosphatasia – with coincident bisphosphonate exposure (*17*).

The authors recognise that this case series is not sufficiently powered to comment on the risk/benefit analysis of bisphosphonates, and that their data lack histomorphometric evidence or markers of bone turnover. The 2006 FLEX study (*2*) suggests that alendronate prevents 200 clinical fractures if 4000 women are treated over 3 years, and will cause one femur fracture over the same course of time. The evidence is insufficient to suggest any causal relationship between oral bisphosphonates and subtrochanteric fractures. No more is there a rationale for linking of other oral bisphosphonates with the evidence already published for alendronate. Men and women with established osteoporosis have a high risk of fragility fractures within the five years after diagnosis, and in these cases the proven benefits of bisphosphonates outweigh the theoretical long-term risks. These benefits, however, are proven only for the first 5 years (*13*). The authors do not suggest any alteration to the primary treatment of osteoporosis with oral bisphosphonates, but feel that their findings add to the emerging concerns about the long term prescription of oral bisphosphonates.

CONCLUSION

Patients who are receiving bisphosphonate therapy and who have a subtrochanteric femoral fracture should be referred to a metabolic bone disease specialist. For patients who are receiving bisphosphonate therapy and who report symptoms of pain originating from the femur, appropriate radiographic examination of both femurs should be performed. In addition, given the frequency of bilateral injuries in this cohort, for patients who have had a subtrochanteric fracture while taking oral bisphosphonates, close surveillance of the contralateral femur is warranted.

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