



# An emerging pattern of subtrochanteric stress fractures: A long-term complication of alendronate therapy?☆

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## KEYWORDS

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Alendronate;  
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Stress fractures;  
Stress reaction;  
Prodromal symptoms;  
Severely suppressed bone turnover

## Summary

**Background:** Subtrochanteric insufficiency fractures in post-menopausal patients have not been commonly reported in the literature. A recent increase in the incidence of such fractures occurring in patients while on alendronate therapy led us to conduct a retrospective review of these patients in our institution.

**Methods:** Seventeen patients, with a mean age of 66 years, sustained low energy subtrochanteric fractures within a 20-month period. These patients were incidentally found to be on alendronate therapy for an average of 4.8 years. Clinical data and history were reviewed and roentgenograms were evaluated by a single investigator. All additional imaging and bone mineral density measurements available were analysed.

**Results:** A characteristic fracture configuration suggestive of an insufficiency stress fracture was identified on plain radiographs. This consisted of (a) cortical thickening in the lateral side of the subtrochanteric region, (b) a transverse fracture, and (c) a medial cortical spike. In addition, 9 (53%) patients had bilateral findings of stress reactions or fractures, and 13 (76%) had symptoms of prodromal pain.

**Conclusions:** These insufficiency fractures could possibly have developed from the over suppression of bone turnover from prolonged alendronate therapy, in keeping with recently published evidence. This study further highlights the need for heightened awareness of alendronate's potential adverse effects.

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☆ The corresponding author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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## Introduction

Subtrochanteric stress fractures are not widely described in the current literature. In the younger age group, fatigue stress fractures in this region are known to occur in runners and athletes.<sup>4,9</sup> Subtrochanteric insufficiency fractures in the older osteoporotic age group have not been commonly reported, and only isolated cases have been mentioned in relation to patients with hypophosphatemic osteomalacia,<sup>6</sup> pycnodysostosis,<sup>14</sup> or in whom fluoride therapy has been prescribed.<sup>16</sup>

We have noticed a recent increase in incidence of these fractures occurring in older patients in our institution who have been receiving alendronate, a potent inhibitor of bone resorption. Most of these fractures resulted from low energy trauma, and some were preceded by prodromal pain in the affected limb.

A retrospective review of these patients was undertaken to determine if a causal relationship with alendronate usage could be established, and to further define this pattern of fractures. We observed a peculiar but consistent fracture configuration that suggested an insufficiency fracture. Moreover, a number of patients had radiological evidence of stress reactions either before the fracture occurred or on the contralateral femur. These findings were all the more unusual given that they were on anti-resorptive therapy for osteoporosis.

## Materials and methods

We retrospectively reviewed all patients admitted to our institution from 1 May 2005 to 31 January 2007 with a low energy subtrochanteric femur fracture whilst on alendronate therapy. Subtrochanteric fracture was defined as a fracture within the region of the femur 5 cm distal to the lesser trochanter. Exclusion criteria included patients with high energy trauma, pathological fractures secondary to underlying malignancies, and subtrochanteric extensions from intertrochanteric fractures. Ethical approval was obtained from the Institutional Review Board prior to commencement of the study.

All clinical data and history were reviewed from case records and via telephone interviews. Roentgenograms were evaluated by a single investigator, and fractures were classified according to the AO comprehensive classification for subtrochanteric fractures (type A: simple transverse or short oblique; type B: comminution with medial or lateral wedge; type C: severe comminution with loss of segmental continuity). Bone mineral density

measurements prior to initiation of alendronate therapy were traced where possible.

Senior orthopaedic surgeons from our institution, using their preferred technique for fixation, carried out surgical fixation of these fractures at the earliest feasible date. Intraoperative specimens were sent for histology to exclude a malignant process in patients where an index of suspicion was present. Bone scintigraphy was also performed in selected patients to exclude bony metastases.

## Results

Seventeen patients were identified in our study group and their details are tabulated in Table 1. All fractures were sustained in low energy circumstances, commonly a fall after tripping, although seven patients (patients 2, 4, 5, 9, 10, 15 and 17) experienced acute pain before the onset of a fall, for example whilst getting up from a chair. All patients were female of Chinese ethnicity, with an age range of 53–82 years (mean age of 66 years).

All patients were receiving alendronate treatment with oral calcium supplementation at the time of fracture, with the exception of patient 17, who was on risedronate for 6 years after 4 years of alendronate therapy. Duration of treatment ranged between 2 and 8 years (average 4.4 years). None of the patients were receiving any other concurrent anti-resorptive therapy, such as hormone replacement therapy. Treatment for the majority of patients was initiated either by their primary physicians or gynaecologists.

Pre-treatment bone mineral density (BMD) diagnoses were available for 16 patients, and are tabulated in Table 2. A BMD diagnosis of osteopenia was made in six patients (median T-score at hip  $-1.35$ ; range  $-0.4$  to  $-1.9$ ) and 10 patients had osteoporosis (median T-score at hip  $-2.85$ ; range  $-2.1$  to  $-3.7$ ). T-scores were not available for some patients due to incomplete medical records. It was also noted that several patients were started on anti-resorptive therapy by their primary physicians as they had previously suffered from other fractures, despite BMD results not clearly in the osteoporotic range.

Significant co-morbidities are listed in Table 1. With the exception of three patients with diabetes mellitus, no patients had thyroid, liver or calcium/phosphate metabolic disorders. Other than patient 4 who was on long-term steroids for chronic eczema, no other identifiable causes for secondary osteoporosis could be found in the remaining patients.

The majority of subtrochanteric fractures were classified as AO type A, with the sole exception being patient 4 who had a small medial wedge

**Table 1** Summary of patient details

S. no.	Biodata		ASA class	Significant co-morbidities	Duration of alendronate (years)	Fracture characteristics		
	Sex	Age				Classification (AO)	Contralateral stress reaction/fracture	Prodromal pain, duration
1	Female	65	2	Alpha thalassaemia minor	4	A	Subtrochanteric stress reaction	Yes, 2 months
2	Female	60	2	Nil	3	A	NA <sup>a</sup>	Yes, 6 months
3	Female	67	2	Hypertension, dyslipidaemia, peptic ulcer disease	3	A	Subtrochanteric stress reaction	Yes, 2 years
4	Female	55	2	Chronic eczema on prednisolone	5	B	Mid-shaft stress reaction	No
5	Female	69	2	Diabetes mellitus	5	A	Subtrochanteric stress fracture	Yes, 2 months
6	Female	82	3	Supraventricular tachycardia	5	A	No	Yes, 6 months
7	Female	69	2	Nil	5	A	No	Yes, 3 months
8	Female	64	2	Nasopharyngeal carcinoma, post-RT panhypopituitarism	5	A	Multiple stress reactions on shaft	Yes, unknown
9	Female	77	2	Diabetes mellitus, hypertension	6	A	NA <sup>a</sup>	Yes, one week
10	Female	69	3	Rheumatoid arthritis, Sjogren's disease, cardiac disease	2	A	NA <sup>a</sup>	Yes, few weeks
11	Female	65	2	Nil	2	A	No	No
12	Female	61	2	Cervical carcinoma	8	A	Femoral shaft stress fracture	Yes, few weeks
13	Female	60	2	Hypertension	6	A	Subtrochanteric stress fracture	Yes, 2 years
14	Female	53	2	Nil	7	A	Subtrochanteric stress reaction	Yes, 9 months
15	Female	63	2	Diabetes mellitus, hypertension	2	A	No	No
16	Female	70	3	Cardiac disease, hypertension, dyslipidaemia, stroke	4	A	No	No
17	Female	74	2	Nil	4 (6 years risedronate)	A	Femoral Shaft Fracture	Yes, 3 months

<sup>a</sup> Patients who had contralateral proximal femur procedures done, e.g. hemiarthroplasty, or in whom there was no available imaging for the contralateral femur.

**Table 2** Summary of pre-treatment bone mineral density measurements

S. no.	Bone mineral density (BMD) diagnosis	Femoral neck T-score	Lumbar spine T-score (L1–L4)	Previous fractures
1	Osteopenia	−1.1	−0.8	Patellar fracture
2	Osteoporosis	Not available	Not available	—
3	Osteopenia	−1.6	−1.2	—
4	Osteoporosis	−2.6	−1.1	—
5	Osteopenia	−1.9	−1.4	—
6	Osteoporosis	Not available	Not available	—
7	Not available	Not available	Not available	—
8	Osteoporosis	−2.1	−2.5	—
9	Osteoporosis	−3.7	−2.9	Left intertrochanteric fracture
10	Osteoporosis	Not available	Not available	Left neck of femur fracture
11	Osteopenia	−0.4	−1.4	—
12	Osteoporosis	−3.1	−3.0	Left femoral shaft fracture
13	Osteoporosis	−2.9	−3.0	Left patellar fracture
14	Osteoporosis	−2.8	−1.9	—
15	Osteopenia	−1.8	−0.9	Left tibial shaft fracture
16	Osteopenia	−0.9	−2.2	Multiple vertebral fractures
17	Osteoporosis	Not available	Not available	Left femur shaft

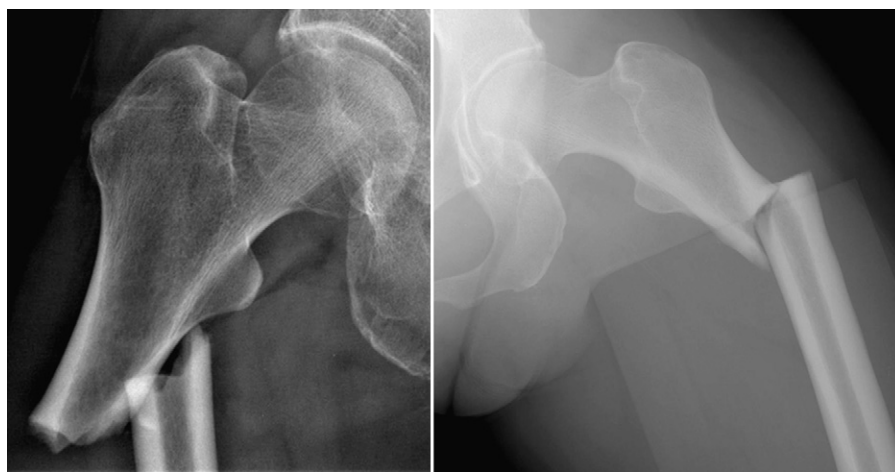
fragment that was classified as an AO type B configuration. Fig. 1 illustrates the typical fracture configuration that we observed in all the patients, consisting of (a) cortical thickening in the lateral (tension) side of the subtrochanteric region, (b) transverse fracture, and (c) medial cortical spike.

In a number of these patients, the development of stress reactions in the subtrochanteric region after the initiation of alendronate therapy can be evidenced on serial plain radiographs (Fig. 2). These stress reactions then progress into complete fractures in the same exact position.

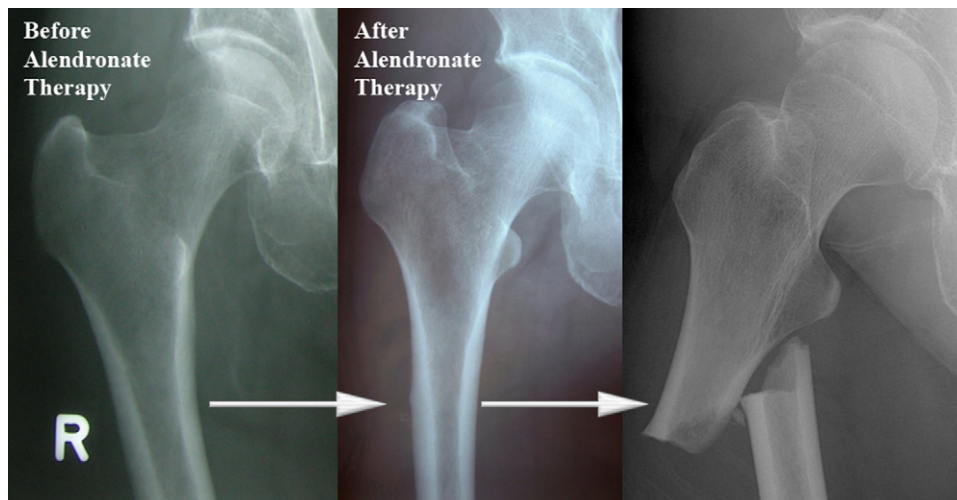
These lateral cortical stress reactions can also be observed on the subtrochanteric region of the contralateral femurs of patients 1, 3 and 14 (Fig. 3). Similar stress reactions could also be seen on the

contralateral femoral shaft of patients 4 and 8 (Fig. 4). Post-operative bone scans were obtained for patients 4 and 13, showing increased activity corresponding to the locations of the stress reactions seen on plain radiographs (Fig. 5). In addition, patient 5 in our series was diagnosed to have a contralateral subtrochanteric stress fracture at the time of presentation.

This 'bilaterality' phenomenon is further illustrated in patients 12, 13 and 17 who sustained bilateral complete femoral fractures. Patient 12 was started on alendronate therapy in 1998. In 2003, she sustained a low energy fracture of her left femoral shaft. After fixation of that fracture, her alendronate was not discontinued. She subsequently sustained a subtrochanteric fracture of her



**Figure 1** Plain radiographs of two patients demonstrating the characteristic fracture configuration of (a) lateral cortical thickening, (b) transverse fracture, and (c) medial cortical spike.



**Figure 2** Serial radiographs showing stress reactions/fractures developing in the subtrochanteric region after initiation of alendronate therapy.

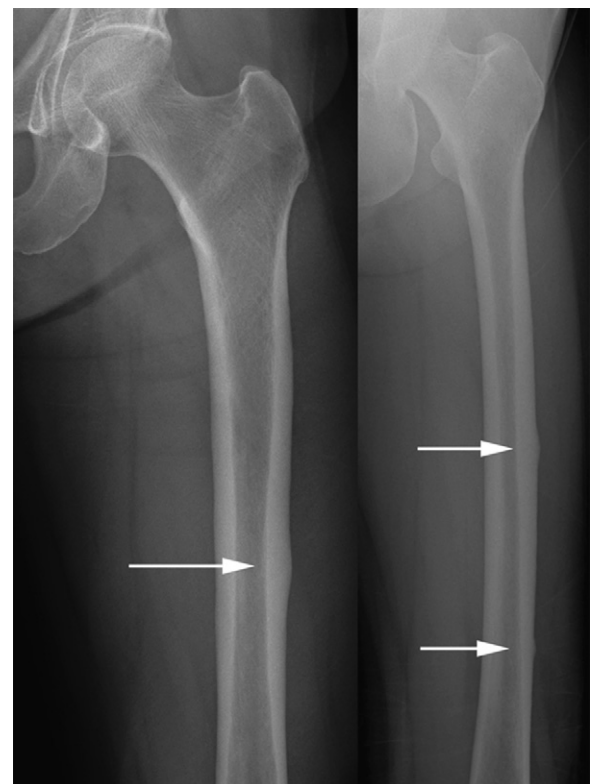
contralateral femur 3 years later in 2006. Patient 13 was placed on alendronate in 2000. In 2004, she sustained a right subtrochanteric fracture, which was fixed. Alendronate was not discontinued and she sustained a contralateral subtrochanteric fracture 2 years later. All fractures shared similar characteristics.

Patient 17 was on alendronate for 4 years before converting to risedronate due to poor response to the original drug. She sustained a mid-shaft fracture of the left femur after 6 years of bisphosphonates therapy, and presented again 4 years later with a subtrochanteric fracture of her contralateral femur. This is the only patient in our study who sustained insufficiency fractures whilst on risedronate therapy, although she did receive prior treatment with alendronate.

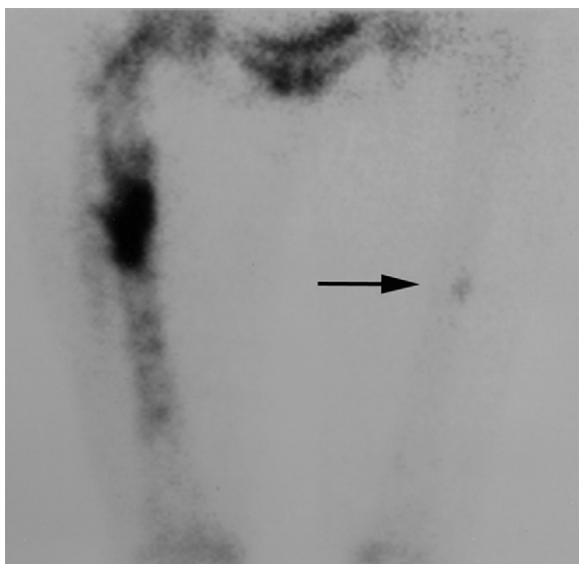


**Figure 3** Plain radiograph showing lateral cortical stress reaction in the contralateral right subtrochanteric region (arrow).

In one patient, we further characterised the lateral cortical stress reaction with CT and MRI imaging. CT imaging showed a 2 cm lateral cortical thickening on coronal cuts and transverse CT cuts demonstrated radiolucent resorption cavities within this lateral cortical thickening. These resorption cavities have been described as early lesions that



**Figure 4** Plain radiographs of patients 4 and 7 with arrows indicating the lateral cortical stress reactions in the contralateral femoral shafts.



**Figure 5** Post-operative bone scintigraphy of patient 4 showing increased uptake in the contralateral left femur corresponding to the positions of the stress reactions evidenced on the plain radiograph.

precede the formation of cortical fractures.<sup>7</sup> MR imaging of the same subtrochanteric region showed marrow insinuating into these lesions with overlying cortical thickening (Fig. 6).

Another interesting finding was that in 13 patients (76%), there were complaints of pre-existing pain in the affected limb prior to the fracture. This prodromal pain ranged from between a week to two years before injury. It was either localised to the anterior or lateral thigh, or groin. One patient characterised it as “weakness” in the leg rather than pain. Often, these patients were treated as for referred pain from a spinal origin without improvement.

## Discussion

Alendronate is a potent inhibitor of osteoclast-mediated bone resorption and is widely used as first-line therapy for the prevention of osteoporotic fractures. It acts by suppressing osteoclastic activity and inducing apoptosis of the osteoclasts.

Alendronate has been shown to significantly increase bone density of the spine and hip,<sup>2</sup> as well as reduce the incidence of osteoporotic fractures by up to 50%. When discontinued after 5 years, the physiological effect on bone resorption remains for 5 years thereafter, with no increase in fracture risk.<sup>3</sup>

However, in recent years, several authors have raised concerns over the potential harmful effects of prolonged bone turnover suppression, particularly for alendronate. Odvina et al reported on nine patients who sustained spontaneous non-spinal fractures while on alendronate therapy, with histomorphometric analysis showing severely suppressed bone turnover (SSBT).<sup>11</sup> She also observed a poor rate of union in these fractures despite discontinuing alendronate therapy, which is in keeping with the findings of the FLEX trial. Odvina’s report included patients with bilateral femoral shaft fractures which is consistent with our findings of bilateral stress fractures involving the cortical regions of the femur.

Two case reports<sup>1,15</sup> describe subtrochanteric fractures occurring in patients on alendronate with a similar pattern of presentation as our own series, and include histomorphometric evidence of severely suppressed bone turnover.

Data from several studies point to a possible pathophysiology behind this phenomenon. Inhibition of osteoclastic mediated bone turnover results



**Figure 6** MRI scans of patient 14’s contralateral subtrochanteric region, further defining the lateral cortical stress reaction. Note the resorption cavities seen on the transverse image, with bone marrow insinuating into these lesions and thinning of the overlying cortex.

in increased mineralisation, which in turn increases the brittleness of the bone.<sup>5</sup> As microcracks tend to colocalize within highly mineralised regions of cortical bone tissue,<sup>17</sup> the subtrochanteric or diaphyseal cortical bone becomes more susceptible to microdamage under physiological loads. With bone remodelling inhibited, microdamage accumulates<sup>10</sup> and in time, stress reactions arise which may develop into stress fractures and eventually complete fractures.

Our data clearly demonstrates these stress regions, and illustrates how they propagate into fractures following minimal or low energy trauma. The consistently identifiable fracture configuration in all our patients has thus far not been recognised in any other pathological condition, and the incidence of bilateral stress reactions and fractures in more than half of our patients points to a systemic disorder like over suppression of bone turnover rather than a localised pathology. These findings mirror that of a recent publication by Goh et al, which drew subjects from our larger clinical group.<sup>8</sup>

We recognise the lack of bone histomorphometry and bone turnover markers in our data. Nevertheless, this particular fracture pattern has not been previously associated with any form of osteomalacia or mineral disorder, and very likely represents a new pattern of pathological fractures.

We also note that several of our osteopenic patients may have been overtreated with alendronate given their BMD results, thus potentially confounding our findings. However, given the widespread availability of anti-resorptive agents, we feel it is important to include these patients in our study to illustrate the importance of judicious administration of these drugs in the primary care setting.

In this study, we are not able to conclude if this propensity for insufficiency fractures is a shared class effect with other bisphosphonates. Although the majority of patients in our series were on alendronate therapy, one patient sustained bilateral femoral fractures after she was converted to risedronate. As this patient received significant lengths of treatment with both drugs, we could not determine if this was an adverse effect related to risedronate or a sustained effect of alendronate after its discontinuation. However this is so far the only case of insufficiency fractures we have observed in patients treated with risedronate.

## Conclusion

Recent concerns on the long-term safety of bisphosphonates and the appropriate duration of therapy have been raised in editorials by Ott.<sup>12,13</sup> This series

is currently the largest collection of fractures attributed to alendronate therapy and offers further evidence that long-term alendronate may have potential harmful effects. This paper adds clinical significance to Odvina et al's findings, and further defines the clinical picture and radiological findings of such fractures.

Whilst our study does not seek to diminish the important role of alendronate in osteoporosis management, it highlights the need for cautious administration of the drug. Overtreatment of osteopenic patients with anti-resorptives should be avoided. Healthcare practitioners should screen patients on alendronate for prodromal symptoms, and consider the use of radiographs to detect the early stress reactions as described herein. In situations where the characteristic subtrochanteric fractures have already developed, physicians should strongly consider discontinuing the drug.

## Conflict of interest statement

No financial or material support has been received or will be received from any commercial party related directly or indirectly to the research and the work. All authors have no potential conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject of this manuscript.

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