

# Sequential non-traumatic femoral shaft fractures in a patient on long-term alendronate

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Fractures associated with osteoporosis are common among elderly people and postmenopausal women. Bisphosphonate is an effective anti-resorptive drug commonly used for the prevention and treatment of osteoporosis. There are, however, concerns about potential side-effects during long-term treatment with alendronate. We report a case where an 82-year-old woman who had been taking alendronate for 10 years presented with two episodes of non-traumatic femoral shaft fracture. An iliac bone biopsy showed severely suppressed bone turnover, suggestive of adynamic bone disease. We suspect the bone turnover suppression was related to the prolonged use of alendronate.

## Introduction

Osteoporosis is a major public health problem, which is increasing as the population ages. In Hong Kong, Chinese women have a 30% lifetime risk of developing at least one osteoporotic fracture.<sup>1</sup> Bisphosphonate (alendronate) has been widely used for the prevention and treatment of postmenopausal osteoporosis during the past 10 years. It has been shown to improve bone density and decrease osteoporotic fractures.<sup>2-7</sup> As bisphosphonate can stay in the bone for a prolonged period, the optimum duration of treatment remains uncertain.<sup>8</sup> There have been concerns about potential over-suppression of bone turnover, and therefore side-effects, during long-term use of alendronate.<sup>9</sup> We present a case of low-energy femoral shaft fractures in a patient who had prolonged alendronate treatment.

## Case report

In March 2006, an 82-year-old woman experienced sudden right thigh pain when walking on the street. She could not bear weight and fell to the ground. Her right thigh was swollen and tender. An X-ray of her right femur showed a transverse fracture at the shaft (Fig 1) and no lytic or sclerotic lesions were seen.

This woman had a bilateral total knee replacement for osteoarthritis in 1999 (ie 7 years before the current fracture). In 2003, she sustained a non-traumatic left femoral shaft fracture, also while walking in the street, which required internal fixation. A dual energy X-ray absorptiometry (DEXA) bone density assessment performed in 2005 measured a T-score of -2.2 and Z-score of 0.1 at the right femur, and a T-score of -2.6 and a Z-score of -0.4 in the anteroposterior lumbar spine. Her only medications included (1) oral alendronate 70 mg weekly for the past 10 years, (2) calcium carbonate 500 mg three times daily for 10 years, (3) glucosamine hydrochloride 500 mg two times daily for 3 years, and (4) chondroitin sulfate 400 mg two times daily for 3 years.

On admission, the alendronate was stopped in view of the possible association between the fracture and long-term bisphosphonate therapy. Calcium and vitamin D supplements were given for her osteoporosis. Biochemical measurements showed normal serum calcium, phosphorus, creatinine, alkaline phosphatase, 25-hydroxy-vitamin D, and urinary calcium levels. Her plasma parathyroid hormone was 9.0 pmol/L (reference range, 1.5-7.6 pmol/L) and her 24-hour urinary creatinine clearance was 72.40 mL/min (reference range, 80-125 mL/min). Her urinary hydroxyproline was 33 µmol/mmol creatinine (reference range, 6-21 µmol/mol creatinine).

Three days after admission, a closed reduction and intramedullary nailing were performed on the fractured right femur. Postoperatively, bony alignment was good.

A bone biopsy using double-tetracycline labelling was performed according to the Bone Metabolic Disease Biopsy Proforma of the Department of Pathology, Princess Margaret Hospital. Before the biopsy, the patient received 250 mg tetracycline four times daily for 2 days, followed by a drug-free period of 12 days, and then 100 mg doxycycline daily for 2 days. A bone biopsy was obtained 4 days later from the anterior superior iliac spine using

### Key words

Alendronate; Diphosphonates; Femur; Osteoporosis; Treatment outcome

*Hong Kong Med J* 2007;13:485-9

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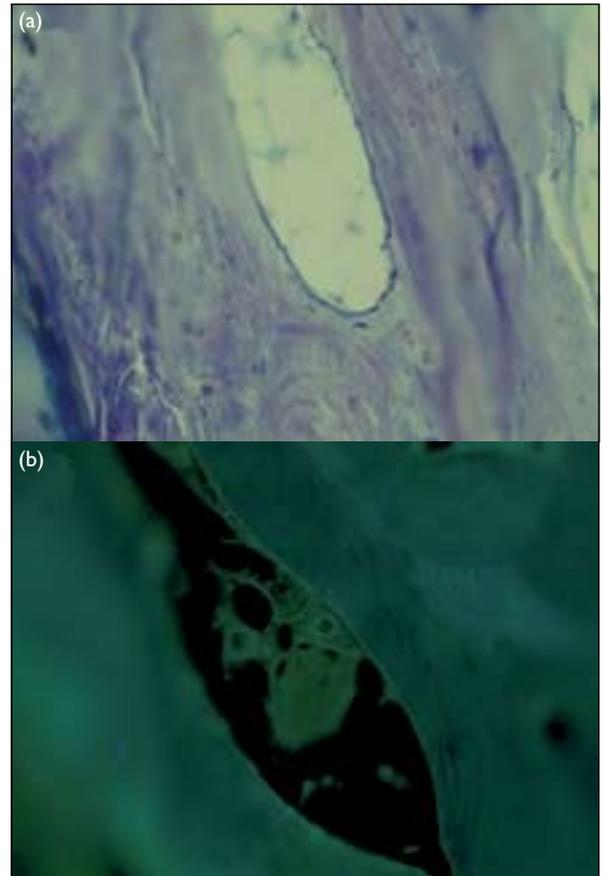
## 長期服用阿倫麟酸鈉病人出現連續非創傷性股骨幹骨折

骨質疏鬆症引致骨折常見於老人和絕經後女性。雙磷酸化合物是一種有效的抗吸收藥，常用於防治骨質疏鬆，但長期施用阿倫麟酸鈉可能引致的副作用卻備受關注。本病例報告描述的就是一位82歲服用阿倫麟酸鈉長達10年的女病人，發生兩次非創傷性股骨幹骨折。髌骨活檢發現，骨轉換嚴重抑制，顯示可能是無動力型骨病，懷疑骨轉換受抑制可能與施用阿倫麟酸鈉時間過長有關。



FIG 1. X-ray of right femur upon admission

a trephine biopsy needle, under local anaesthesia. The specimen was fixed in absolute alcohol and sent to the laboratory, which reported that the biopsy showed severely suppressed bone turnover (SSBT), suggestive of adynamic bone disease. Under microscopic examination, sections showed pieces of cancellous bone with many of the trabeculae having a mostly smooth outline. The trabeculae were covered by very thin osteoid, accounting for about 40% of their surface. The average osteoid thickness was only 1.068  $\mu\text{m}$ . The osteoid volume was only 0.428% of the bone volume. There was no conspicuous osteoblastic or osteoclastic activity. The erosion surface/bone surface ratio was zero. There was no paratrabecular fibrosis (Fig 2a). The tetracycline stain showed no double labelling (Fig 2b). The iron stain was positive in the marrow space but the aluminium stain was negative. A congo red stain for amyloid was negative.



(c) Parameters of bone formations	
Bone volume (bone volume/total volume, %)	48.206
Osteoid thickness ( $\mu\text{m}$ )	1.068
Osteoid volume/bone volume (%)	0.428
Osteoid surface/bone surface (%)	39.5
Parameters of bone resorption	
Erosion surface/bone surface (%)	0
Osteoclast number/bone area (/cm)	0
Osteoclast surface/bone surface (%)	0
Dynamic studies	
Mineral apposition rate/day ( $\mu\text{m}/\text{day}$ )	No values
Mineralising surface/osteoid surface (%)	No values
Mineralisation lag time (days)	No values
Osteoid maturation time (days)	No values

FIG 2. Pathological findings from iliac bone biopsy (a) Light microscopy showing trabeculae covered by very thin osteoid; there were no conspicuous osteoblastic or osteoclastic activities (toluidine blue,  $\times 400$ ). (b) Fluorescence microscopy with ultraviolet excitation showing absence of tetracycline label. (c) Histomorphometric results of iliac bone biopsy

Results of the bone histomorphometry are shown in Fig 2c.

A bone scan, performed later, showed increased uptake over the right femur, left femur, and

left anterior ilium. The bony lesions were compatible with operative sites and old or new fractures. The bilateral total knee replacement was observed.

Upon discharge, the patient was able to tolerate quadripod walking and the calcium and vitamin D supplements were continued.

## Discussion

This case report describes a relatively healthy postmenopausal woman who had been taking long-term alendronate for osteoporosis. She experienced two non-traumatic femoral shaft fractures 3 years apart.

Osteoporosis is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bony tissue, with a consequent increase in bone fragility and susceptibility to fractures. Our patient was osteoporotic, a state confirmed by DEXA.

Osteoporotic fractures are low-energy fractures that involve the hip, vertebra, distal forearm, proximal humerus, pelvis, or proximal tibia. They do not commonly occur at the femoral diaphysis. On the other hand, femoral shaft fractures occur most frequently in young patients after high-energy trauma. The bending force needed to produce a femoral shaft fracture in a normal adult has been estimated at 250 Nm, and may exceed 8000 Nm in purely axial compression.<sup>10</sup> Our patient sustained a low-energy transverse fracture of the bone while she was walking on the street, suggesting that the bone had to be weakened to produce such an unusual fracture.

The cause of her fracture was elucidated by bone histomorphometry. Her bone biopsy showed that bone formation was severely depressed, with marked reduction in osteoid thickness and osteoid volume. Although 40% of the trabeculae surface was covered by osteoid, the osteoid was very thin. Together with a normal 25-hydroxy-vitamin D level, the possibility of osteomalacia was excluded. There were no bony resorptive activities. There was no double labelling on tetracycline staining, and the tetracycline scarcely appeared as a thin fluorescent line. The two tetracycline cycles were given in separate oral doses, with no gastro-intestinal intolerance, in an in-patient setting. The bone biopsy was performed 4 days after the last dose of tetracycline to minimise error in the fixation process. Together with the finding of overall deficiency of osteoid volume, this absence of double tetracycline labelling indicated a mineralisation deficiency. There was no conspicuous osteoclastic activity. The erosive surface was minimal and osteoclasts were not found in any measurable manner. These findings did not support a diagnosis of hyperparathyroidism. Her marginally elevated plasma parathyroid hormone may be due to diurnal

variation but the cause remains uncertain. Overall, the bone biopsy showed SSBT.

Severely suppressed bone turnover is defined histologically by reduced osteoblastic and osteoclastic surfaces, with decreased or absent tetracycline labelling. When bone turnover is markedly suppressed, the bone cannot repair microcracks that occur after stresses encountered in day-to-day life. The damage accumulates and eventually weakens the bone. It is characterised clinically by non-traumatic fractures that usually occur at atypical sites such as femoral shafts, the pubic bone and ischium.<sup>9,11</sup> Our patient did not have chronic renal failure, hypoparathyroidism, and was not on glucocorticoid treatment or oestrogen therapy that could account for the low bone turnover. Although her urine hydroxyproline level was not low, this marker has poor sensitivity and specificity for assessing bone resorption.<sup>12</sup> Hydroxyproline is a collagen degradation product. Only half of the urinary content originates from bone. It is also affected by diet and can be elevated during fracture healing. The clinical picture and investigation results together raised concerns that the long-term bisphosphonate (alendronate) treatment may have led to SSBT and the unusual fractures.

Bisphosphonates have been widely used and recommended for prevention and treatment of osteoporosis.<sup>13</sup> Alendronate is the bisphosphonate most widely used for osteoporosis therapy. It is important to understand the mechanism of action of this class of drugs in order to interpret their beneficial skeletal effects and potential side-effects. They are synthetic pyrophosphate analogues that bind to hydroxyapatite crystals in bone. When used therapeutically, they inhibit osteoclast function and promote osteoclast apoptosis. Postmenopausal osteoporosis is caused by an increase in bone resorption outstripping bone formation, thus the inhibition of bone resorption produces a net increase in bone mass in the first year or two of bisphosphonate use. After that, bone cells signal to one another to maintain appropriate resorption-formation coupling. The rate of bone formation eventually decreases to equal that of resorption, leading to an overall reduction in bone turnover. The bone mass tends to stabilise and an increased degree of mineralisation is allowed. These features, in principle, contribute to the anti-fracture properties of bisphosphonates.<sup>14</sup>

Bone turnover and remodelling are considered a natural part of maintaining bone health. With long-term alendronate, profound suppression of bone turnover may occur, which may result in microdamage accumulation and cause the bone to become more brittle. This could possibly lead to an increase in the fracture rate.<sup>9,11</sup>

Clinical trials have shown that both vertebral

and non-vertebral fractures are reduced after receiving alendronate for 3 to 4 years,<sup>2-4</sup> but long-term fracture data are lacking.<sup>8</sup> In studies of those taking alendronate for a longer period, possible beneficial skeletal effects have been suggested by an increase in bone mineral density and suppression of bone turnover markers.<sup>5-7</sup> Nevertheless, resistance to fractures is related to bone density, the turnover rate, microarchitecture, geometry, and mineralisation. Measurements of surrogate markers alone may not represent an ultimate decrease in the fracture rate and it has not been established that there is any benefit from taking the drug for more than 5 years.<sup>8,11</sup>

Odvina et al<sup>9</sup> reported on nine osteoporotic or osteopaenic patients who presented with spontaneous non-spinal fractures (femoral shaft, sacrum, rib, ischium, pubic rami) while taking alendronate at the usual dosage for 3 to 8 years. Six of the patients displayed delayed fracture healing. Histomorphometric analyses of cancellous bone biopsies showed severe suppression of bone formation, with absence of double-tetracycline labelling. The SSBT resembled the adynamic bone disease that was present in some patients on chronic maintenance haemodialysis. The author concluded that alendronate can potentially cause SSBT, resulting in increased susceptibility to non-spinal fractures that heal poorly.

A later case report described similar non-traumatic fractures in atypical sites in a patient who took long-term alendronate.<sup>15</sup>

It is noteworthy that alendronate has prolonged

bony retention and the biochemical effect of the drug is dosage-related.<sup>16</sup> Bioavailability of the drug also varies substantially with respect to timing of meals, the effect of beverages and gastric pH.<sup>17</sup> Therefore, bone turnover suppression by the drug is likely to be related to dosage and patient factors. These may explain why severe bone turnover suppression occurs in only some individuals after long-term alendronate, while some studies have found no obvious defects in mineralisation or bone quality after use of the drug.<sup>18,19</sup>

We advise clinicians to be aware of the potential side-effects of SSBT in some patients who take long-term alendronate. When there are unusual fractures and suspected SSBT in such patients, the drug should be stopped. It would have been reasonable to stop the drug when our patient was treated for a non-traumatic left femoral shaft fracture in 2003.

## Conclusion

Bisphosphonates are useful for treating osteoporosis but there are concerns that long-term use of alendronate treatment may lead to SSBT and unusual fractures. The patient in this report took long-term alendronate and sustained two non-traumatic femoral shaft fractures, with biopsy-proven SSBT. Vigilant surveillance and more research on the long-term effects of bisphosphonates are needed.

## Declaration

The authors declared no conflicts of interest.

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