Subtrochanteric insufficiency fractures in patients on alendronate therapy

A CAUTION


From Singapore General Hospital, Republic of Singapore

We carried out a retrospective review over ten months of patients who had presented with a low-energy subtrochanteric fracture. We identified 13 women of whom nine were on long-term alendronate therapy and four were not. The patients treated with alendronate were younger, with a mean age of 66.9 years (55 to 82) vs 80.3 years (64 to 92) and were more socially active. The fractures sustained by the patients in the alendronate group were mainly at the femoral metaphyseal-diaphyseal junction and many had occurred after minimal trauma. Five of these patients had prodromal pain in the affected hip in the months preceding the fall, and three demonstrated a stress reaction in the cortex in the contralateral femur.

Our study suggests that prolonged suppression of bone remodelling with alendronate may be associated with a new form of insufficiency fracture of the femur. We believe that this finding is important and indicates the need for caution in the long-term use of alendronate in the treatment of osteoporosis.

Alendronate is a potent inhibitor of bone resorption and was the first drug of its class to be approved for use in the prevention of osteoporotic fractures by the USA Food and Drug Administration in 1995.1 In two randomised controlled studies, treatment with alendronate has been shown to decrease the incidence of vertebral and femoral-neck fractures in post menopausal osteoporotic patients.2,3 We also prescribe it as a first-line treatment for patients with osteoporosis. There are now a considerable number of patients who have been taking alendronate for at least five years. The medication is excluded from health-service subsidy and the full cost has to be borne by the patient. It is thus only really available to the upper socioeconomic classes.

We have observed an apparent rise in the number of subtrochanteric fractures of the femur in women aged between 50 and 70 years after minimal or no trauma. Many of these patients had been receiving alendronate for at least three years.

We considered that it was unusual for patients receiving alendronate to sustain such fractures so easily. In an attempt to establish if there is a link between the two we reviewed all low-energy subtrochanteric fractures presenting to our department over a period of ten months, and compared the patients who were taking alendronate or had been taking it within one year of a fracture, with those who were not.

Patients and Methods

Between 1 May 2005 and 28 February 2006 we carried out a retrospective review of the operating records of all orthopaedic surgeons from two hospitals (Singapore General Hospital and Changi General Hospital, Republic of Singapore) to identify patients who had been treated surgically for subtrochanteric fracture of the femur. A subtrochanteric fracture was defined as one in the region of the femur which extended from the lesser trochanter to the junction of the proximal and middle third of the femoral shaft. We included only fractures sustained in low energy trauma and excluded those due to a car accident, a fall from a height or underlying malignancy. Ethical approval was obtained from the Institutional Review Board before the study was commenced.

We identified 13 women with a subtrochanteric fracture which had been sustained by low-energy trauma. Details of the patients are given in Table I. There were nine women who had been taking alendronate, and four who had not. The patients in the alendronate group were younger, with a mean age of 66.9 years (55 to 82) vs 80.3 years (64 to 92).

Case records of the patients were reviewed to determine the mechanism of injury, the pres-
2.5 SDs below the young adult peak BMD.5 defines osteoporosis as a BMD value more than 2.5 SDs below that of the young adult peak BMD known as the "gold standard". Measurements were performed on the femoral neck and L1 to L4 vertebral bodies. The World Health Organisation (WHO) recommends using dual-energy x-ray absorptiometry (DEXA) for these measurements.

Prior to, or after the fracture. The measurements were available for some of the patients within a year either before or after the fracture. Radiographs were reviewed by three authors (S-KG, JSBK, TSH) to classify the patterns of the fracture according to the AO classification. When necessary, the patients were also interviewed to ascertain the details of their symptoms and pharmacological history.

### Table I. Details of the 13 patients

<table>
<thead>
<tr>
<th>Alendronate</th>
<th>No alendronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>9</td>
</tr>
<tr>
<td>Mean age in yrs (range)</td>
<td>66.9 (55 to 82)</td>
</tr>
<tr>
<td>AO classification of subtrochanteric fracture</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>8</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
</tr>
<tr>
<td>Mean duration of alendronate therapy in yrs (range)</td>
<td>4.2 (2.5 to 5)</td>
</tr>
</tbody>
</table>

### Fracture configurations.

In the alendronate group eight of the patients had AO type-A fractures occurring at the metaphyseal-diaphyseal junction while the ninth had a type-B fracture. In six, cortical hypertrophy was identified on the lateral, tension side of the subtrochanteric region of the femur (Figs 1 and 2). In three, a similar hypertrophied cortex could be seen in the contralateral subtrochanteric region (Fig. 3).

Three patients in the non-alendronate group had an AO type-B fracture and one a type-C fracture (Fig. 4). As judged on the plain radiographs, the bones appeared to be extremely osteoporotic with the loss of the trabecular pattern.

### Discussion

Pauwels6 was the first to identify that the subtrochanteric region of the femur is subjected to maximal bending movement. As such, this area is one of the strongest parts of the femur and it is unlikely to fail in low-energy trauma, unless extreme osteoporosis is present. It has been estimated that only 10% to 34% of all fractures of the hip are in the subtrochanteric region.7

The patients in the alendronate group were striking for several reasons. All had received alendronate and oral calcium therapy for a mean of 4.2 years (2.5 to 5), yet the trauma which these nine patients had sustained was minimal, a few had experienced prodromal pain in the months preceding the fracture and lastly, most were in the early stages of the menopause and had led relatively active lifestyles at the time of injury.

Alendronate belongs to the family of bisphosphonate drugs which are stable synthetic analogues of pyrophosphate characterised by a phosphorous-carbon-phosphorus bond.8 The administration of bisphosphonates, as a group, is one of the first-line treatments for the prevention of osteoporotic fractures in menopausal patients.9 The Fracture Intervention Trial10 study showed that patients who were taking alendronate had a reduced risk of sustaining an ence or absence of prodromal pain before the fracture, the bone mineral density (BMD) if available, the past medical history, the histological findings of bone from the site of the fracture when available, and the administration of alendronate within a year of the fracture. Radiographs were reviewed by three authors (S-KG, JSBK, TSH) to classify the patterns of the fracture according to the AO classification (Table II), and to look for abnormality in the contralateral limb. There was complete agreement on all classifications. When necessary, the patients were also interviewed by telephone to ascertain the details of their symptoms and pharmacological history.

### Table II. Comprehensive AO classification of subtrochanteric fractures4

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Simple transverse or short oblique fracture</td>
</tr>
<tr>
<td>B</td>
<td>Comminution in the form of a medial or lateral wedge fragment</td>
</tr>
<tr>
<td>C</td>
<td>Severe comminution representing a segmental loss of continuity</td>
</tr>
</tbody>
</table>

### Proximal symptoms.

In the alendronate group five patients reported experiencing pain or discomfort in the fractured limb, between two and six months before the injury, one of whom had prodromal pain in the groin on the fractured side, whereas the remainder localised the pain at the lateral aspect of the thigh. By contrast, none of the patients in the non-alendronate group had prodromal symptoms.

### History of treatment with alendronate.

Nine patients were taking alendronate and oral calcium for treatment of osteoporosis either at the time, or within the year before the injury. Of the four patients who were not currently taking alendronate, two were taking oral calcium supplements. The data concerning the administration of alendronate, and the BMD of the patients (when available) are given in Table IV.

### Fracture configurations.

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Three patients in the non-alendronate group had an AO type-B fracture and one a type-C fracture (Fig. 4). As judged on the plain radiographs, the bones appeared to be extremely osteoporotic with the loss of the trabecular pattern.

### Histological findings.

In five patients in the alendronate group, bone biopsies were sent intra-operatively for histological analysis to exclude neoplasia. All were found to be benign.

No histological specimens were sent from the four patients who were not taking alendronate because there was radiological evidence of severe osteoporosis in each.

### Discussion

Pauwels6 was the first to identify that the subtrochanteric region of the femur is subjected to maximal bending movement. As such, this area is one of the strongest parts of the femur and it is unlikely to fail in low-energy trauma, unless extreme osteoporosis is present. It has been estimated that only 10% to 34% of all fractures of the hip are in the subtrochanteric region.7

The patients in the alendronate group were striking for several reasons. All had received alendronate and oral calcium therapy for a mean of 4.2 years (2.5 to 5), the trauma which these nine patients had sustained was minimal, a few had experienced prodromal pain in the months preceding the fracture and lastly, most were in the early stages of the menopause and had led relatively active lifestyles at the time of injury.

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osteoporotic fracture at a follow-up of three years. It has also been proven that alendronate therapy is associated with an increase in BMD in osteoporotic patients. This effect was sustained throughout the duration of alendronate therapy when administered for up to ten years. Alendronate inhibits bone resorption by suppressing the activity of osteoclasts, and inducing them to undergo apoptosis. While this leads to an increase in the BMD of patients with osteoporosis, treatment with alendronate has also been shown to reduce the amount of bone turnover. In animal experiments concern has been expressed that alendronate therapy can lead to the accumulation of skeletal microdamage. In humans, prolonged administration of intravenous pamidronate can lead to the development of osteopetrosis or marble bone disease. This microdamage may increase the risk of insufficiency fractures.

The fractures in the alendronate group were all simple, mostly AO type-A subtrochanteric fractures in patients who had radiologically good cortical bone stock. This contrasts with the radiological findings seen in patients who were not taking alendronate. It is interesting that thickening in the lateral femoral cortex was present in six of the alendronate patients, and in three of these the cortical thickening was bilateral. This, and the history of prodromal pain, lend support to the possibility that these were insufficiency fractures which possibly resulted from altered bone metabolism.

This is the first report to document a series of fractures in the subtrochanteric region of the femur in patients who were receiving alendronate for a long period. However, our study certainly does not establish cause and effect. Indeed, many of these patients were originally on alendronate and calcium therapy because they were at a higher risk for

### Table III. Biomedical data and mechanism of injury in all 13 patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Mechanism</th>
<th>Co-morbidities</th>
<th>Presence and duration of prodromal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>Tripped and fell</td>
<td>Alpha thalassaemia minor, hysterectomy and ovarectomy</td>
<td>Yes, 2 months</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>Heard a crack in the thigh while retrieving a shot during badminton</td>
<td>Nil</td>
<td>Yes, 6 months</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>Fell down three stairs and landed on buttocks</td>
<td>Nil</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>Right-anterior thigh pain after tripping awkwardly while crossing road</td>
<td>Eczema, on long-term oral steroids</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>Heard a crack while shopping</td>
<td>Diabetes mellitus. Cervical and lumbar spondylosis</td>
<td>Yes, 2 months</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>Right hip pain after fall</td>
<td>Supraventricular tachycardia, Mycoplasma pneumonia</td>
<td>Yes, 6 months</td>
</tr>
<tr>
<td>7</td>
<td>69</td>
<td>Slipped and fell on to buttocks</td>
<td>Hysterectomy and ovarectomy, Cervical and lumbar spondylosis</td>
<td>Yes, 3 months</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>Fractured femur while walking down stairs</td>
<td>Nasopharyngeal carcinoma, 10 years previously Parhypopituitarism, Ischaemic heart disease</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>71</td>
<td>Tripped and fell while shopping</td>
<td>Osteoarthritis knees</td>
<td>No</td>
</tr>
<tr>
<td>No alendronate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>92</td>
<td>Fell after vertiginous episode</td>
<td>Hypertension, Hypothyroidism, Hypertension, renal failure and osteoedystrophy Diabetes mellitus</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>Tripped and fell while walking</td>
<td>No</td>
<td></td>
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<tr>
<td>3</td>
<td>86</td>
<td>Fell after being pushed by grandson</td>
<td>Peptic ulcer disease, Patellofemoral arthritis</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>79</td>
<td>Slipped and fell in kitchen</td>
<td>Nil</td>
<td>No</td>
</tr>
</tbody>
</table>

### Table IV. The bone mineral density (BMD) status of the alendronate patients and the duration of treatment at the time of the injury.

<table>
<thead>
<tr>
<th>Case</th>
<th>Year of DEXA scan</th>
<th>Left femoral neck T-score</th>
<th>Lumbar spine T-score</th>
<th>Diagnosis</th>
<th>Alendronate duration (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2003</td>
<td>-1.1</td>
<td>-0.8</td>
<td>Osteopenia</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>2005</td>
<td>-1.6</td>
<td>-1.2</td>
<td>Osteopenia</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>2005</td>
<td>-2.1</td>
<td>-1.1</td>
<td>Osteopenia</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>5</td>
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<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>2005</td>
<td>-2.1</td>
<td>-2.5</td>
<td>Osteoporosis</td>
<td>5</td>
</tr>
<tr>
<td>9*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

* unable to give details of BMD status
osteoporotic fractures. Nevertheless, our findings identify a potential, originally unrecognised, side-effect of prolonged pharmacological suppression of bone turnover.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References


