A rational approach to management of alendronate-related subtrochanteric fractures

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There have been recent reports linking alendronate and a specific pattern of subtrochanteric insufficiency fracture. We performed a retrospective review of all subtrochanteric fractures admitted to our institution between 2001 and 2007. There were 20 patients who met the inclusion criteria, 12 of whom were on long-term alendronate. Alendronate-associated fractures tend to be bilateral (Fisher’s exact test, p = 0.018), have unique radiological features (p < 0.0005), be associated radiologically with a pre-existing ellipsoid thickening of the lateral femoral cortex and are likely to be preceded by prodromal pain. Biomechanical investigations did not suggest overt metabolic bone disease. Only one patient on alendronate had osteoporosis prior to the start of therapy. We used these findings to develop a management protocol to optimise fracture healing. We also advocate careful surveillance in individuals at-risk, and present our experience with screening and prophylactic fixation in selected patients.

The past decade has seen the increasing use of bisphosphonates for prevention of fractures associated with osteoporosis. Alendronate was the first bisphosphonate to be approved for use in this manner and has been shown to reduce the incidence of vertebral and hip fractures in post-menopausal women with osteoporosis.1-3

A recent suggestion that bisphosphonates may be related to severe suppression of bone turnover which results in insufficiency fractures at unusual sites has raised questions about the use of anti-resorptive therapy.4-11 Although these studies suggest an association between bisphosphonates and insufficiency fractures, it is evident that this class of drug is invaluable in reducing the risk of osteoporotic fractures. In order to better delineate the role of bisphosphonates, as well as the management of patients with purported severe suppression of bone turnover, we performed a retrospective review to identify the unique characteristics of such insufficiency fractures. Based on these findings, we developed institutional management guidelines for patients at risk of this phenomenon. It is hoped that the results of this study and our experience with optimising fracture healing as well as fracture prevention, will raise awareness among both orthopaedic surgeons and non-orthopaedic physicians regarding the range of treatment options available, while dispelling the notion that bisphosphonates are universally harmful.

Patients and Methods

We undertook a retrospective study of all subtrochanteric fractures receiving surgical treatment in our institution between January 2001 and December 2007. The subtrochanteric region was defined as the area between the inferior border of the lesser trochanter and the junction of the proximal and middle third of the femur. High-energy injuries and obvious pathological fractures were excluded. We assessed all the available medical records for information on comorbidities, details of alendronate therapy, relevant investigations, surgical treatment and outcome. Where available, radiographs taken prior to fracture were also reviewed. In the event of insufficient data, patients were contacted by telephone to clarify discrepancies or obtain additional information.

From our initial observations and published reports5,6 we noted that alendronate-associated subtrochanteric fractures were either transverse or slightly oblique, with minimal comminution and marked thickening of the lateral cortex (Fig. 1). Plain anteroposterior radiographs of the pelvis of all subjects in our study were reviewed by three orthopaedic surgeons including two authors (TS, SDD) who were blinded to whether the patients had received alendronate and were asked to identify if unique radiological features were present. An additional control group of 136 patients with inter-trochanteric fractures of the...
femur who had not received bisphosphonates were reviewed for morphometric abnormalities of the proximal femur.

The details of the patients are summarised in Table I. The Mann-Whitney U test was used to compare the categorical data between patients on alendronate therapy and those who were not, and the chi-squared test or Fisher’s exact test were applied to compare the nominal observations. The associations between alendronate usage, bilateral fractures and the radiological features were assessed by the chi-squared test or Fisher’s exact test as applicable.

As this was a retrospective study, not all patients had had radiographs taken before their fracture. In such cases we assumed that the presence of a lateral cortical thickening at the fracture site suggested the presence of a pre-existing structural abnormality.

Results

Patient demographics. We identified 51 patients with subtrochanteric fractures, 20 of whom had low-velocity injuries due to a fall. There were 19 women and one man. All were of Chinese ethnicity, and their mean age was 63.1 years (44 to 88). Of these there were 12 patients who had received 70 mg of alendronate for a weekly mean duration of 4.6 years (3 to 8.5). Whether there was pain or instability prior to the fall could not be reliably ascertained owing to the retrospective nature of the study. There was no significant difference in age, gender or the mechanism of injury in patients who were on long-term alendronate compared to those who were not.

Bilateral fractures. There were six patients in the alendronate group with bilateral fractures, giving a total of 26, but no bilateral injuries in those not receiving this drug. Four of the contralateral fractures were complete; the remaining two were stress fractures identified on bone scintigraphy scans. Of the contralateral fractures, five were in the subtrochanteric femur and one in the mid-shaft. In five patients the contralateral fracture occurred within three to five years of the first. In the other patient there was simultaneous fracture of both subtrochanteric regions after she felt her legs ‘give way’, while walking.

Radiological features. The fractures associated with long-term alendronate therapy had a unique fracture configuration (Fig. 1). Thickening of the lateral femoral cortex with widening and ‘splaying’ of the fracture ends was seen in 11 of the 12 patients on alendronate, but not in the eight patients who were not taking alendronate (Fisher’s exact test, p < 0.0005). In addition, a transverse or slightly oblique, non-comminuted fracture pattern was seen in 11 of the 12 patients on long-term alendronate, compared with one of the eight who were not (Fisher’s exact test, p = 0.001).

Pre-existing radiological changes. To confirm the hypothesis that the presence of lateral cortical thickening at the site of the fracture suggested a pre-existing structural abnormality, we reviewed all available radiographs of the femurs taken before the fracture in our cohort of subtrochanteric fracture, including those of the contralateral side. An ellipsoid thickening in the lateral cortex was noted in nine femurs (Fig. 2). All of these patients were on long-term alendronate therapy. Five of these progressed to complete fracture, four subtrochanteric, one mid-shaft of the contralateral femur. Among the remaining four patients, two had thigh pain and bone scintigraphy demonstrated stress fractures that were prophylactically fixed before a complete fracture could develop (Table II). The remaining two patients were being followed-up for treated subtrochanteric fractures, and the pelvic radiographs demonstrated an ellipsoid thickening in the opposite asymptomatic femur. One of them had not sustained a contralateral fracture after three years. She had stopped taking alendronate and there was regression of the lateral cortical thickening. The other patient was only followed for a year before she died from unrelated causes.

All seven patients with the ellipsoid thickening who sustained a complete or stress fracture reported prodromal hip or thigh pain. Owing to the retrospective nature of the study, prodromal pain was impossible to ascertain in those who did not have pre-fracture radiographs without introducing significant recall bias.

Morphometry of the proximal femur in the Asian population. The 136 patients from the control group had a higher mean age (77 years, 56 to 93) and included 87 women. Among them, 117 were of Chinese ethnicity and the rest...
approximately equally divided between Indians and Malays. These patients had sustained femoral inter-trochanteric fractures, and none were on bisphosphonates prior to fracture. A review of both the affected and contralateral femurs did not reveal any ellipsoid thickening of the lateral femoral cortex such as those observed in the alendronate-related fracture group, suggesting that neither ethnicity or gender were related to this structural abnormality.

Biochemical investigations. All available markers relevant to bone turnover and metabolic bone disease, including the serum alkaline phosphatase, calcium, phosphate, parathyroid hormone, vitamin D and thyroid function tests, were evaluated. Sixteen of the 20 patients had these investigations performed, but there was no suggestion of underlying metabolic bone disease such as osteomalacia in either the alendronate or the non-alendronate group.

Bone mineral density scores. Table I indicates the bone mineral density (BMD) scores in our cohort at the time of fracture. Of the nine patients with BMD scores, seven had their first BMD scans at the time of fracture. Only two patients on prednisolone for Behçet’s disease and post-renal transplant immunosuppression had BMD scans prior to fracture. None of the patients had sustained fractures at the hip, spine or wrist before the subtrochanteric fracture. It is therefore evident that 11 of the 12 patients on alendronate had no documented evidence of decreased bone density prior to initiation of bisphosphonate therapy, which questions the indication for such therapy.

Fracture union and complications. Three patients in the alendronate group had nonunion of their fracture, presenting as pain and/or breakage of the implant, which required revision of the fixation and bone grafting. There was only one case of nonunion requiring further surgery in the non-alendronate group (Table I).

Discussion

Current understanding of alendronate-related subtrochanteric fractures: is alendronate truly to blame? The subtrochanteric femur is subject to some of the highest stresses in the body, and one of the adaptations to such forces is the high content of cortical bone in this region. Subtrochanteric fractures after low-velocity injuries are therefore rare, and usually associated with an underlying weakening of the bone. In our study, the higher incidence of bilateral frac-

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### Table I. Patient characteristics

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Duration of alendronate therapy (yrs)</th>
<th>Other anti-resorptive therapy</th>
<th>BMD at femoral neck (T-score)</th>
<th>BMD diagnosis (WHO definition)</th>
<th>Type of operative fixation</th>
<th>Complications requiring further surgery</th>
<th>Bilateral femur fracture</th>
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<tbody>
<tr>
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<td>57</td>
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<td>-2.29</td>
<td>Osteopaenia</td>
<td>EM DCS</td>
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<td>66</td>
<td>4</td>
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<td>-</td>
<td>Osteopaenia</td>
<td>IM IM nail</td>
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<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>8</td>
<td>No</td>
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<td>Osteopaenia</td>
<td>EM DCS</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>3</td>
<td>Prednisolone (rheumatoid arthritis)</td>
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<td>Osteoporosis</td>
<td>EM DCS</td>
<td>Nil</td>
<td>No</td>
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<td>5</td>
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<td>4</td>
<td>Prednisolone (Behçet’s)</td>
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<td>EM DCS</td>
<td>Nil</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>5</td>
<td>No</td>
<td>-2.00</td>
<td>Osteopaenia</td>
<td>IM IM nail</td>
<td>Nil</td>
<td>Not known</td>
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<td>7</td>
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<td>4</td>
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<td>-1.29</td>
<td>Osteopaenia</td>
<td>IM IM nail</td>
<td>Nil</td>
<td>Yes</td>
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<tr>
<td>8</td>
<td>70</td>
<td>7</td>
<td>No</td>
<td>-1.48</td>
<td>Osteopaenia</td>
<td>EM DCS</td>
<td>No</td>
<td></td>
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<tr>
<td>9</td>
<td>75</td>
<td>4</td>
<td>No</td>
<td>-</td>
<td>Osteopaenia</td>
<td>EM DCS</td>
<td>Non-union</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>3</td>
<td>Prednisolone (post-renal transplant)</td>
<td>-</td>
<td>Osteopaenia</td>
<td>EM ABP</td>
<td>No</td>
<td></td>
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<tr>
<td>11</td>
<td>63</td>
<td>4</td>
<td>No</td>
<td>-</td>
<td>Osteopaenia</td>
<td>EM DCS</td>
<td>Non-union, implant cut-out</td>
<td>Yes</td>
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<tr>
<td>12</td>
<td>61</td>
<td>4</td>
<td>No</td>
<td>-</td>
<td>Osteopaenia</td>
<td>IM IM nail</td>
<td>Nil</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BMD, bone mineral density; EM, extramedullary device; IM, intramedullary device; DCS, dynamic condylar screw; ABP, angled blade plate; DHS, dynamic hip screw; gamma, gamma nail
models.13-18 Animal studies involving risedronate and turnover has also been reported in several animal long-term alendronate treatment and suppressed bone remodelling.15,17 Tang et al18 and Seigmund, Allen and incadronate have also demonstrated similar effects on bone collagen-type 1 (NTx), are decreased.4,11 The association of faces, with reduced or absent tetracycline labelling.4,11,13-17 histologically by reduced osteoblastic and osteoclastic sur-

severe suppression of bone turnover, a condition defined specific alkaline phosphatase and urinary milieu where markers of bone turnover, such as bone-spe-
cific alkaline phosphatase and urinary N-telopeptides of collagen-type 1 (NTx), are decreased.4,11 The association of long-term alendronate treatment and suppressed bone turnover has also been reported in several animal models.13-18 Animal studies involving risedronate and incadronate have also demonstrated similar effects on bone remodelling.15,17 Tang et al18 and Seigmund, Allen and Burr19 have shown that high doses of bisphosphonates result in accumulation of advanced glycation end-products through a process of non-enzymatic glycation, which renders cortical bone more brittle and liable to fracture.

We describe one of the largest series of alendronate-related subtrochanteric fractures, with 18 treated over a seven-year period in a tertiary hospital. These fractures are, however, rare, considering that approximately 180 patients are admitted annually to our institution with fractures of either the neck or inter-trochanteric region of the femur. The low incidence of such fractures among a much larger population of patients taking alendronate might suggest that genetic factors related to bone metabolism and cellular response to bisphosphonates may be the underlying pathomechanism of severe suppression of bone turnover. It is possible that certain patients may already have pre-existing micro-architectural changes like a greater proportion of non-enzymatically cross-linked collagen, that make them more likely to sustain insufficiency fractures after initiation of bisphosphonates by aggravation rather than as a causative factor. In addition, the dose and duration of alendronate therapy may not correlate to the risk of fracture, as the drug tends to persist in the body for several years after discontinuation of treatment.20-22

Significance of pre-existing radiological abnormality. The ellipsoid thickening observed prior to fracture in patients on alendronate probably represents a suboptimal osteoblastic response to physiological microfractures, with the production of a larger callus with greater mineral content but less lamellar bone.16 When the microfractures accumulate and propagate beyond a critical level, clinical manifestations of structural instability develop, such as pain, and precede the complete fracture. The observed radiological features must be distinguished from the Looser zones which are seen in osteomalacia. The latter are broad lucent bands perpendicular to the cortex, with minimal or absent callus or sclerosis, and present mainly on the compressed medullary cortex.23 In contrast the thickening seen in our patients is sclerotic, without a band of central lucency, and on the lateral, tension, aspect of the cortex. In our series, this radiological feature seemed to correlate strongly with alendronate usage, with no relation to ethnicity or gender and none of these patients had features of underlying osteomalacia. The consistency of the bone noted at surgery was extremely hard and sclerotic, similar to that seen in osteopetrosis, resulting in breakage of the drill bit in one case.

Management of alendronate-related subtrochanteric fractures. Although these fractures are already predisposed to nonunion and delayed union,12 our series and other studies suggest a slightly higher incidence of nonunion with alendronate usage.4,16 We therefore suggest fixation with an intramedullary device and partial to full weight-bearing post-operatively. In situations where a nail cannot be used, such as with an extremely narrow canal in an individual of short stature, open plating must be performed. An iliac crest biopsy may also be obtained for histomorphometric analysis. Our preferences for the management of patients with alendronate-related subtrochanteric fractures are summarised in Figure 3.

Optimisation of bone density and prevention of further fractures in patients on long-term alendronate. A disturbing observation in our series was the unwarranted prescription of bisphosphonates. This may reflect a flawed perception of these drugs as ‘health supplements’ with minimal adverse effects. Until further evidence is available, bisphosphonates should be discontinued in patients with suspected severe suppression of bone turnover. There is evidence to suggest that recombinant parathyroid hormone (e.g. teriparatide) may improve bone turnover and microarchitecture in patients on long-term alendronate, and this might be initiated post-operatively.24,25 Bisphosphonate therapy should be reserved either for patients
with established osteoporosis or for osteopenic patients with fractures at the wrist, hip and vertebra, in accordance with established international or institutional guidelines. An endocrinologist may be consulted in the management of such patients. Any patient on long-term bisphosphonates with a normal or mildly abnormal BMD study should be urged to discontinue the medication. An assessment of fracture risk can be made using the WHO Fracture Risk Assessment Tool, FRAX. This enables the physician to analyse risk objectively by considering multiple population-specific risk factors, and thus decide on anti-resorptive therapy.

**Surveillance of patients with prior alendronate-related fractures.** We recommend careful surveillance of patients with a prior alendronate-related femoral fracture, given the significant incidence of bilateral fractures in this group (Fig. 3). Radiographs of the contralateral femur are obtained at the time of fracture and should be repeated if there is pain in the opposite limb. An MRI or bone scan should also be considered if there is suspicion of a stress fracture.

The main reasons for advocating surveillance in this population of patients are the increased risk of developing subsequent insufficiency fractures, the use of clinical
examination and radiographs in identifying individuals at risk and preventing the adverse sequelae of complete fractures, such as delayed union, nonunion and implant breakage through prophylactic surgical fixation. A planned elective procedure will also have less psychosocial impact on the patient than an emergency admission after a complete fracture.

The true incidence of the observed radiological abnormality in the entire population of patients on alendronate is unknown, and it is entirely possible that a proportion of patients on long-term alendronate may have lateral cortical thickening but never progress to fracture. Because of this, screening all patients on long-term alendronate with routine radiographs is not cost-effective and may cause widespread panic. However, the development of groin or thigh pain in a patient on long-term alendronate should prompt further work-up with radiographs and bone scintigraphy.

**Table II. Prophylactic fixation of alendronate-related stress fractures: our experience**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Comorbidities</th>
<th>Duration of alendronate therapy (yrs)</th>
<th>Prodromal pain (duration)</th>
<th>Ellipsoid lateral cortical thickening (location)</th>
<th>BMD diagnosis (WHO definition)</th>
<th>Bone scan</th>
<th>Type of operative fixation</th>
<th>Post-operative complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>F</td>
<td>Nil</td>
<td>4</td>
<td>No</td>
<td>Yes (2 months) Yes (ST)</td>
<td>Nil</td>
<td>Increased uptake at ST region</td>
<td>DCS</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>F</td>
<td>HT, HL, DM, CVA, Gout, gastritis, renal calculi, goitre</td>
<td>6</td>
<td>No</td>
<td>Yes (12 months) Yes (mid-shaft)</td>
<td>Nil</td>
<td>Increased uptake at mid-shaft</td>
<td>IM</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>F</td>
<td>HT, DM, HL, trigeminal neuralgia</td>
<td>4</td>
<td>No</td>
<td>Yes (8 months) Yes (ST)</td>
<td>Osteopenia</td>
<td>Increased uptake at ST region</td>
<td>IM</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>F</td>
<td>RA, HT, HL, IHD, CVA, lumbar spinal stenosis, OA knees, cataracts, DVT</td>
<td>8</td>
<td>Yes (prednisolone) Yes (2 days)</td>
<td>Yes (ST)</td>
<td>Osteoporosis</td>
<td>Increased uptake at ST region</td>
<td>DCS</td>
<td>No</td>
</tr>
</tbody>
</table>

HT, hypertension; DM, diabetes mellitus; HL, hyperlipidaemia; CVA, cerebrovascular accident; RA, rheumatoid arthritis; IHD, ischaemic heart disease; OA, osteoarthritis; DVT, deep vein thrombosis; ST, subtrochanteric; BMD, bone mineral density; DCS, dynamic condylar screw; IM, intramedullary nail

* Patient developed contralateral thigh pain while on follow-up after treatment of a complete subtrochanteric insufficiency fracture. Although the ellipsoid thickening was noted in the mid-shaft of the femur, the radiological findings were identical to those seen in the subtrochanteric region.

Radiographs showing prophylactic fixation of alendronate-related stress fracture of the subtrochanteric femur, in a) a 64-year-old woman presented with increasing right lateral thigh pain over eight months with a worsening limp. She had been on alendronate for four years, although bone mineral density scans demonstrated mild osteopenia. Clinical examination revealed a full range of movement at the right hip, but an inability to load the limb, with a positive Trendelenburg sign. Radiographs revealed an ellipsoid thickening in the right subtrochanteric region, b) bone scintigraphy indicated intense tracer uptake in the right subtrochanteric region, corresponding to the area of thickening on the pelvic radiograph and c) prophylactic fixation was performed using an intramedullary nail. The patient began mobilising with a walking frame the following day, and was able to climb a flight of stairs with minimal pain on the third day. On review eight months after surgery she was asymptomatic. There was an ellipsoid thickening noted on the left femur, which resulted in a complete fracture two years later, before prophylactic fixation could be performed.
MRI or bone scintigraphic evidence of stress fracture and prior subtrochanteric or femoral shaft fracture, with the unique fracture configuration described in Figure 1. The risk-benefit considerations must be thoroughly explained to the patient prior to surgery, as the decision to undergo operation may be justifiably difficult, particularly in a patient without a prior fracture. Asymptomatic patients with radiological abnormalities may be observed closely, as prophylactic surgery may not be justified in the absence of functional impairment. A recent report by Capeci and Tejwani\textsuperscript{27} suggests a similar approach to patients with such fractures.

In our series, two patients had previously sustained a complete subtrochanteric fracture and were on routine follow-up and the other two presented with persistent pain for the first time. All had been on alendronate for at least four years. Radiographs indicated an ellipsoid thickening on the lateral cortex and bone scintigraphy scans confirmed stress fracture. Prophylactic fixation was performed with extramedullary devices in two patients as the medullary canals were too narrow to permit a nail. Immediate full weight-bearing was commenced, and all the patients were walking independently at the time of discharge from hospital. The duration of follow-up after surgery was eight, 13, 20 and 60 months and there were no complications related to the implant or healing. Alendronate therapy has been stopped in this group of patients.

Limitations of the study. Owing to the retrospective nature of this study, one limitation was that pre-fracture radiographs were not available for some patients, and in this group the presence of lateral cortical thickening of the fracture site was taken to represent a pre-existing radiological abnormality. It was difficult to assess retrospectively the presence of prodromal pain in patients who had already presented with a fracture. These data could therefore only be evaluated in patients who had been assessed by a specialist prior to the injury. A further limitation is that bone biopsy specimens were not available for histomorphometric analysis. More data are also required to identify the population at risk accurately, as not all individuals on alendronate therapy will develop cortical thickening or an insufficiency fracture. Finally, the optimum length of surveillance after cessation of alendronate needs to be determined.

Alendronate-related subtrochanteric fractures are probably due to underlying metabolic and micro-architectural changes that render the bone less resistant to physiological stresses. These fractures are rare, suggesting underlying genetic and pre-existing architectural differences as possible contributory factors. They usually occur after three to four years of alendronate therapy, tend to be associated with prodromal pain and are frequently bilateral. They are also associated with a specific pre-existing radiological abnormality that may develop several years prior to fracture. We recommend management guidelines that aim to optimise the outcome after such fractures, as well as prevent the occurrence of subsequent fractures through the rational and cost-effective use of anabolic agents, clinical assessment tools, judicious screening, and prophylactic fixation in selected patients.

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


