An older woman on bisphosphonate therapy who continues to fracture

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Antiosteoporotic therapies reduce fracture rates but do not eliminate fractures completely. A proportion of patients will continue to fracture despite adequate osteoprotective medications, counselling and support. There are multiple factors that contribute to recurrent fractures and careful evaluation is required.

Case scenario

Ellen, aged 67 years, fractured her right hip when she fell at the supermarket. Spinal x-ray demonstrated a T6 vertebral wedge fracture and total hip bone mineral density (BMD) T-score measured -3.5 (Z-score of -1.1). She was prescribed daily calcium, vitamin D_3 and weekly oral bisphosphonate therapy.

After 15 months of therapy, Ellen was admitted to hospital for incapacitating thoracic back pain that occurred after she was unloading her shopping from the boot of her car. A repeat spinal x-ray showed the pre-existing vertebral fracture and a new T7 fracture corresponding to the site of her pain.

Ellen's height is 160 cm, she weighs 55 kg and her body mass index is 21.5 kg/m^2. She does not smoke or abuse alcohol. She has never received systemic glucocorticoids and does not have rheumatoid arthritis or any causes of secondary osteoporosis. Her mother experienced a fractured hip at age 81 years.

The following questions should be considered and are discussed in this article:

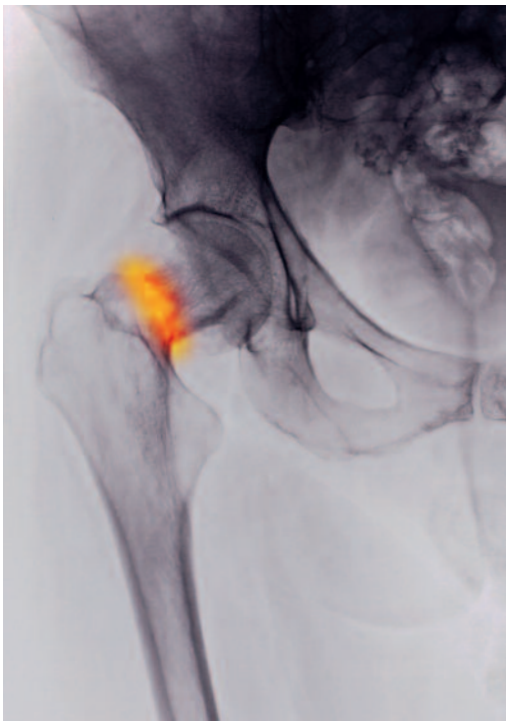
- *Has Ellen's osteoprotective medication failed?*
- *What factors may have contributed to Ellen's recurrent fractures?*
- *How can first fractures be prevented?*
- *What investigations would you consider?*
- *How can Ellen's future fracture risk be reduced?*

Has Ellen's osteoprotective medication failed?

All antiosteoporotic therapies have been shown to be effective in randomised clinical trials demonstrating fracture risk reductions of 25 to 70%.[1] More specifically, oral antiresorptive agents such as the bisphosphonates, hormone replacement therapy and selective oestrogen receptor agonists increase spinal BMD by 4 to 8% and reduce vertebral fracture rates by 30 to 50%.[2] The relative fracture risk reduction on therapy is not 100% and other strategies including lifestyle modification and falls prevention are also important.

Ellen has severe osteoporosis, which is defined as a BMD T-score of -2.5 or less in the presence of one or more fragility fractures. Using the Garvan Institute fracture risk calculator (see: www.garvan.org.au/bone-fracture-risk) that combines BMD with other clinical risk factors, her absolute five-year fracture risk is 61.9% at the hip and 63.6% for any other fragility fracture (see the box on page 23 for Ellen's risk of fragility fracture).[3]

Although Ellen and her family may understandably feel that the osteoprotective medication has 'failed', Ellen may have fractured sooner or had a more devastating fracture without therapy.



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Key points

- **Antiosteoporotic therapies reduce fracture rates but do not eliminate fractures completely.**
- **Beyond the severity of osteoporosis and previous history of fragility fractures, there are multiple other factors that may contribute to recurrent fractures while taking treatment. These include poor therapeutic adherence, suboptimal calcium and vitamin D intake, lifestyle factors such as smoking and excess alcohol consumption, frequent falls and secondary causes of osteoporosis.**
- **The management of osteoporosis begins by recognition of risk factors and appropriate screening.**
- **Patients with severe osteoporosis should be considered for more active antiosteoporotic therapies.**

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What factors may have contributed to Ellen's recurrent fractures?

With each osteoporotic fracture the risk of subsequent fracture increases, also known as the 'fracture cascade' (see Figure).[2,4,5] Fracture at any site is a strong predictor for subsequent fractures in older men and women.[3] Nearly one in five patients with a minimal trauma fracture will experience another event within the next two years.[6] Recurrent fractures significantly impact on a patient's psychological and physical well-being and ultimately contribute to loss of quality of life. In addition, osteoporotic fractures of the spine, hip and indeed all major fragility fractures are associated with premature mortality.[3,7]

Beyond the severity of osteoporosis and previous history of fragility fractures, there are multiple other factors that may contribute to recurrent fractures on treatment. These include poor therapeutic adherence, suboptimal calcium and vitamin D intake, lifestyle factors such as smoking and excess alcohol consumption, frequent falls and secondary causes of osteoporosis.[4]

Therapeutic adherence

Ellen may not have been complying with her osteoprotective medication or may not have been taking it correctly. Ellen did get the initial scripts but may not have filled it, taken the tablets or taken the tablets correctly as prescribed. Clues to nonadherence include not filling prescriptions, deteriorating BMD and increased bone turnover markers (degradation products of type 1 collagen such as amino or carboxy terminal telopeptides or urinary deoxypyridinolone excretion rates).[4]

Long-term compliance with oral bisphosphonates is generally poor. More than 50% of patients do not take their bisphosphonates as directed and less than 40% of women persist with long-term therapy.[4,8] A study investigating nonadherence and fracture rates in 35,537 women showed that women who missed one weekly dose per month over a 12-month period had 64% less fracture protection whereas those who missed half of their doses had 94% less protection.[9,10] The impact of medication nonadherence should not be underestimated and the reasons for noncompliance must be carefully explored. These can include drug side effects such as heartburn, gastrointestinal upset, bone pain and skin rashes.[11]

Patients need to comply with strict dosage instructions because many of the oral bisphosphonates are poorly absorbed from the gut and need to be taken on an empty stomach in an erect position to avoid oesophageal irritation and at least 30 minutes before a meal. Once-weekly (alendronate and risedronate) and once-monthly (risedronate) oral regimens, twice-yearly subcutaneous humanised antibody against receptor activator of NF-κB (RANK) ligand (denosumab) and the once-yearly parenteral infusion (zoledronic acid) may improve medication compliance.[4]

Ellen's risk of fragility fracture

Ellen's five-year risk of fragility fracture is at least 60% because she has osteoporosis (T-score of total hip = -3.5), a history of more than one fragility fracture (right hip and two vertebral fractures) and a history of parental hip fracture, the most reliable indicator of genetic predisposition to osteoporosis.[3]

If her osteoprotective medication were as effective as reported in clinical trials, this risk would be reduced by about 50% (i.e. from 60 to 30%).

The following is a simple way to estimate her approximate risk over any specific period – e.g. 18 months:

18 months is three-tenths of five years

Her five-year risk is 30%

Therefore, her 18-month risk is three-tenths of 30% = 9%*

*This risk is nonlinear, however, and is highest within the first 12 months after spinal fracture.

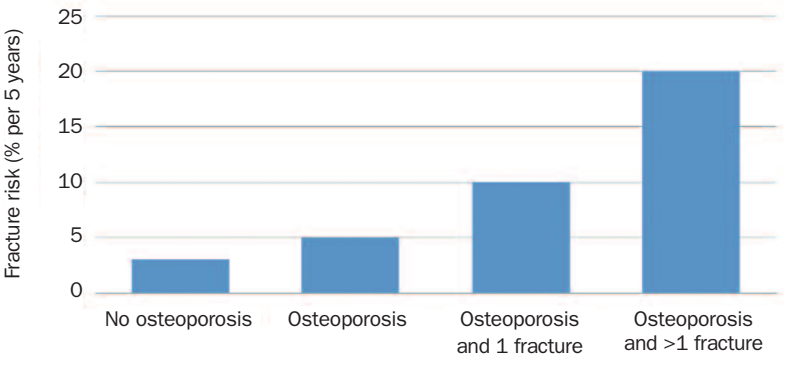

Figure. Osteoporosis fracture risk in women >60 years of age.[5]

Calcium and vitamin D

The efficacy of antiosteoporotic therapies requires adequate dietary calcium intake and vitamin D levels. Serum levels of 25-hydroxyvitamin D of 50 to 75 nmol/L and above are the target, which usually requires maintenance doses of 800 IU /day or more.[4] People with mild to moderate vitamin D deficiency require a dose of 3000 to 5000 IU/day for at least six weeks.[4] Combination preparations of an oral bisphosphonate with cholecalciferol may increase drug adherence. Concurrent calcium intake of at least 1200 mg/day with antiosteoporotic agents is also required for skeletal efficacy.[1,4] Given current debate regarding cardiovascular complications, adequate dietary rather than supplemental calcium is recommended first line as well as the use of calcium with vitamin D supplementation rather than calcium supplementation alone.[12]

Assessment after fragility fracture

Assess severity of osteoporosis

- Clinical risk factors: age, parental hip fracture, lifestyle factors (e.g. alcohol consumption and smoking history), chronic comorbidities, secondary causes
- BMD: T and Z-scores. T-score value of -1.5 to -2.5 indicates osteopenia. T-score of -2.5 or less indicates osteoporosis. Z-score of -2.0 or less requires further investigations to exclude secondary causes of osteoporosis
- History of fragility fractures
- Spinal x-ray for silent vertebral fractures
- Medication review to identify drugs that may impair normal bone remodelling (e.g. antiepileptic drugs, thyroxine excess, corticosteroids, aromatase inhibitors, glitazones, selective serotonin reuptake inhibitors)

Assess therapeutic compliance

- History
- Prescriptions filled
- Medication taken as directed
- Bone turnover markers may be considered (deoxypyridinoline excretion rates and C-terminal and N-terminal telopeptides of type 1 collagen)

Check adequate calcium and vitamin D

- Serum 25-hydroxyvitamin D levels: <50 nmol/L increase risk of fragility fractures[19]

Assess lifestyle risk factors

- Cessation of smoking and excessive alcohol consumption
- Calcium-rich diet
- Adequate sun exposure. For fair skinned people 6 to 8 minutes before 10 am and after 2 pm in summer, and 15 to 30 minutes at noon in winter depending on latitude. People with pigmented skin require exposure times 3 to 4 times greater[20]
- Weight-bearing exercise

Assess risk of falls

- Medication review to identify drugs that may increase risk of falls (anticholinergics, antihypertensives, psychotropic medications)
- Occupational therapist home assessment
- Modification of behavioural risk factors (e.g. use of aids)
- Balance retraining programs

Evaluate for secondary causes of osteoporosis

Recurrent falls

Recurrent falls increase fracture risk. Risk factors for falls include impairment of vision, sensation, strength and balance, inadequate nutrition, sarcopenia, cognitive impairment, neurological disease and polypharmacy.[13] A meta-analysis of falls prevention trials has demonstrated that mulitfactorial falls risk assessment and prevention programs are most effective at reducing falls.[3,4] Vitamin D supplementation in the institutionalised elderly also reduces falls[14] most likely due to preservation of normal muscle function.

Secondary causes of osteoporosis

Ellen may have a secondary cause of osteoporosis that was overlooked or subclinical 15 months earlier. This should be considered given the severity of her osteoporosis, although her Z-score of greater than -2.0 makes this less likely.

Secondary osteoporosis should be considered in women older than 40 years of age who experience a minimal trauma fracture and those with a BMD Z-score of less than -2.0.[4] Although postmenopausal osteoporosis is common, 20 to 40% of these women will have secondary causes contributing to their bone fragility – that is, causes other than menopause-related ovarian failure and oestrogen deficiency.[15] Secondary causes include use of medications (e.g. corticosteroids, aromatase inhibitors, glitazones, antiepileptic drugs) that can impair normal bone remodelling, as well as medical disorders, including hyperthyroidism, primary hyperparathyroidism, malabsorptive states, such as coeliac disease, and malignancies including multiple myeloma and breast cancer.[15] Carefully screening for, and in some cases removing, these secondary causes of osteoporosis may obviate the need for long-term antiosteoporotic therapies.

Antiosteoporotic agent-related abnormal bone remodelling

The coupling of osteoblast and osteoclast activity is vital for microfracture repair and normal bone health.[16] Antiresorptive agents lead to uncoupled bone remodelling whereby osteoclasts are inhibited while osteoblast activity continues.[4] Owing to the long bone half-life of bisphosphonates, their protracted use has been proposed to cause marked suppression of bone turnover leading to hypermineralised bones which in turn predisposes to atypical fractures.[17] However, the causal relation between this pathophysiology and atypical fractures continues to be debated.

It is unlikely that adynamic bone disease contributed to Ellen's recurrent fractures given her limited duration of antiresorptive therapy and the location of her fracture in the spine.

How can first fractures be prevented?

As osteoporosis is an insidious disease the diagnosis is often not made until after the first clinical fracture. The fracture cascade model highlights the importance of preventing this first fracture and the important role of GPs in screening patients at risk. The key risk factors identified by three major international guidelines include low BMD, past history of fracture, age, gender and multiple falls.[3] Other risk factors include smoking, immobility and low body weight.[3]

What investigations would you consider?

The osteoporosis syndrome includes several different components and therefore medical assessment is multifaceted (see the box on this page).[18-20] Assessment should also include the impact of the fracture in terms of pain,

disability and dependence, and the consequential effects on self-confidence, psychological well-being, social networking and quality of life. This assessment may require contributions from specialist allied health and/or nursing staff and may prompt a GP management plan and Team Care Arrangement to organise and oversee allied health involvement in the rehabilitation process.

Team Care Arrangement might include:

- a three-monthly medical review of the osteoporosis syndrome to identify and address physical and psychosocial problems that may arise, as well as ongoing assessment for fragility fracture risk factors (for example, falls risk assessment)
- a six-monthly Home Medicines Review to assess compliance with pharmaceutical administration instructions, to identify nonadherence and to observe for potential drug side effects
- ongoing involvement of agencies that can provide support in the community.

How can Ellen's future fracture risk be reduced?

Overview of assessment

The management of osteoporosis begins by recognition of risk factors and appropriate screening. The prescription of an antiosteoporotic agent, cholecalciferol and calcium must be coupled with encouragement and education regarding appropriate drug administration and the importance of therapeutic adherence.[4] Lifestyle factors including cessation of tobacco and alcohol use, as well as regular weight-bearing exercise, should also be addressed.

Patients who continue to fracture on treatment must be assessed for noncompliance, falls risk and secondary causes of osteoporosis. Progress BMD and bone turnover markers may be helpful in determining compliance or efficacy.[4] People with severe osteoporosis or with fractures after taking long-term antiresorptive therapy will benefit from specialist opinion.

Treatment of severe osteoporosis

Ellen should be considered for more active therapy with an anabolic agent given her T-score of less than -3.0, presence of two previous fractures secondary to minimal trauma as well as a new fracture despite 12 months of antiresorptive therapy. Parathyroid hormone (1-34) fragment, teriparatide, which is an anabolic agent, can reduce fracture risk by up to 70%.[21] It is available on the PBS (authority required) for severe established osteoporosis in a patient at high risk of fracture for an 18-month period (see the full schedule). Concurrent treatment with vitamin D_3 and calcium supplements must continue; however, all antiresorptive agents are ceased during this period. Monitoring is required for hypercalcaemia. This course of therapy should be followed by antiresorptive therapy to maintain whatever bone mass that has been gained during this treatment.

Denosumab, a potent antiresorptive agent, is another agent that could be considered for Ellen. It is available on the PBS (authority required) for women aged 70 years or older with a BMD T-score of -3.0 or less, or women with established postmenopausal osteoporosis with fracture due to minimal trauma. It is administered every six months via subcutaneous injection. There have been no reports to date of atypical fractures or osteonecrosis of the jaw on the 60 mg six-monthly regimen. Hypocalcaemia has been reported. The main differences between denosumab and the bisphosphonates include reversibility given that the antibody is not incorporated into the bone mineral matrix, lack of gastrointestinal side effects and twice-yearly subcutaneous dosing, which may improve compliance.[12] The pharmacokinetics of denosumab are also unaffected by renal impairment allowing its potential use in patients with chronic kidney disease. Studies have shown rapid return of high bone turnover rates if denosumab is suspended for more than six months after the last dose.[12] Hence, patient follow up is important, as is timely commencement of an alternative antiosteoporotic treatment if denosumab is discontinued.[12]

Useful web resources

Fracture risk calculators

- Garvan fracture risk calculator (www.garvan.org.au/bone-fracture-risk)
- FRAX calculator from Sheffield, UK (www.sheffield.ac.uk/FRAX)

Patient resources and websites

- Australian and New Zealand Bone and Mineral Society (www.anzbms.org.au)
- Australian Menopause Society (www.menopause.org.au)
- Osteoporosis Australia (www.osteoporosis.org.au)
- International Osteoporosis Foundation (www.osteofound.org)

Summary

Antiosteoporotic therapies reduce fracture rates but do not prevent fractures completely. A proportion of patients will therefore continue to fracture despite adherence to therapy. With each osteoporotic fracture the risk of subsequent fracture increases. Hence, primary prevention and active intervention after a fracture event is essential. Useful web resources on osteoporosis are listed in the box on this page.

Multiple factors contribute to recurrent fractures including poor therapeutic adherence, suboptimal calcium intake and vitamin D levels, lifestyle factors, such as smoking and excess alcohol consumption, frequent falls and secondary causes of osteoporosis. Recurrent falls are an important target for fracture risk reduction. Patients with severe osteoporosis should be considered for more active antiosteoporotic therapies. ET

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A list of references is available on request to the editorial office.

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