

An update on osteoporosis

Simple strategies for the prevention of osteoporosis continue to be underutilised, and a fitter elderly population with higher individual bone mineral density could potentially reduce the incidence of morbidity due to osteoporosis.

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The World Health Organization (WHO) has defined osteoporosis on the basis of low bone mineral density (BMD) or the occurrence of minimal trauma fracture.

A low bone mass (or mineral density) is the principal risk factor for low-energy fractures. As bone mass naturally declines with age, the prevalence of osteoporosis and its attendant complications is steadily increasing in Australia's ageing population, with significant implications for individuals and the community health burden (Figure 1).¹

Osteoporosis is underdiagnosed and undertreated. The past decade has seen enormous research activity into the pathophysiology and treatment of osteoporosis, and therapeutic guidelines are still evolving. This article outlines some of the principal developments that have occurred recently in the diagnosis and management, including prevention, of osteoporosis.

Aetiology

Osteoporosis itself is generally considered to be an asymptomatic condition. However, fractures – which occur when the force applied to a bone exceeds its inherent strength – are often associated with pain, deformity, disability and increased mortality.² BMD, age and gender are important factors in predicting absolute fracture risk and influence bone strength and the propensity to falls due to, for example, postural instability (Table 1). A bone's geometry, connective tissue matrix and mineral content determine its strength and, therefore, factors that influence bone strength in a manner independent from BMD (such as a family history of osteoporotic fracture) are important co-predictors for fracture risk.³

Bone is continually being remodelled at a microscopic level by successive cycles of osteoclast-mediated resorption and osteoblast-mediated

IN SUMMARY

- **Assessment of bone mineral density (BMD) by dual energy x-ray absorptiometry (DXA) remains the gold standard for diagnosis of osteoporosis.**
- **General lifestyle measures in the prevention and management of osteoporosis include adequate calcium intake, regular weight-bearing exercise and avoidance of smoking and excess alcohol intake.**
- **Patients with a previous minimal trauma fracture should receive potent antiresorptive therapy to prevent further fracture.**
- **In the absence of fracture, treatment decisions should be based on the severity of osteopenia and the presence of other risk factors including age, gender, family history and risk of falls.**
- **The oral bisphosphonates alendronate and risedronate and the selective oestrogen receptor modulator raloxifene increase BMD and reduce fractures in osteoporotic patients.**
- **Hormone replacement therapy (HRT) increases BMD but its effect on fracture prevention is less clear. Calcitriol is no longer recommended as first line treatment of osteoporosis.**

formation. Oestrogen deficiency after the menopause leads to accelerated bone turnover such that resorption exceeds bone formation, which over time leads to progressive bone loss. Existing therapies for osteoporosis inhibit bone resorption, slowing bone turnover and facilitating remineralisation which leads to increased bone density.⁴

Diagnosis

A number of modalities are now available for the screening and diagnosis of osteoporosis. Dual energy x-ray absorptiometry (DXA) remains the accepted standard, mainly because of the large amounts of normative data and established literature relating to fracture risk that are available and its low radiation dose and good accuracy and precision characteristics. The issue of who to test has important ramifications for targeting preventive strategies effectively, and there is some evidence that a finding of low bone mass by DXA enhances compliance with lifestyle measures and medications. Guidelines regarding when to perform DXA have been well covered in recent articles in this and other journals.^{4,5}

A DXA report should give three values for both the lumbar spine and the hip:

- the BMD of the region
- the relation of the BMD value to the mean gender-matched young adult BMD value (the T-score) in terms of standard deviation units
- the relation of the BMD value to the mean BMD values of gender- and age-matched controls (the Z-score) in terms of standard deviation units.

The T-score is used for diagnosis of osteoporosis (defined as a T-score of at least 2.5 standard deviation units below the young adult normal mean, i.e. a T-score below -2.5) and osteopenia (T-score below -1). A low Z-score (for instance, below -2) may be useful in identifying patients with underlying diseases causing osteoporosis. The absolute BMD value is the best measure for serial follow up in response to treatment.

Other diagnostic modalities – such as forearm DXA, calcaneal ultrasound and spinal quantitative CT – are becoming more widely available. Spinal quantitative CT may have a particular role for accurate measurement of lumbar spine BMD in patients with degenerative spine disease (in

Osteoporosis

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Osteoporosis affects the entire skeleton and fractures may occur in any bone, although the most common sites are the hip, vertebrae, distal forearm, proximal humerus, ribs and pelvis. It is often underdiagnosed and undertreated.

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Table 1. Major risk factors for osteoporotic fractures

Previous minimal trauma fracture

Increases relative risk (RR) for femoral neck fracture by a factor of 1.5

Low BMD

Doubles RR for femoral neck fracture per standard deviation below young adult mean BMD, e.g. if T-score is -2, then RR increases fourfold

Age over 65 years

Increases RR for femoral neck fracture by a factor of 1.5 for each 5 years over age 65

Female sex

Doubles RR for femoral neck fracture (until age 80)

Family history

Maternal hip fracture doubles RR for femoral neck fracture

continued



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Figure 1 (above). False-colour scanning electron micrograph of the trabeculae in bone affected by osteoporosis.



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Figure 2 (right). X-ray of the lumbar spine of a 65-year-old woman showing vertebral damage due to osteoporosis.

whom BMD by DXA is overestimated), but because of its expense and higher radiation dose is not recommended for routine testing. Forearm DXA is less expensive and more readily accessible in some areas; it may be useful for case finding, but a positive finding should be followed up by confirmatory DXA of the lumbar spine and the hip. Calcaneal ultrasound identifies bone quality independently of the mineral content, and may in the future complement DXA in the assessment of fracture risk. At present, however, it is a research tool.

Vertebral fractures may be asymptomatic in up to 30% of cases, but still lead to deformity, loss of height and increased risk of future vertebral and hip fracture.⁶ Thoracolumbar spine radiology may be useful in identifying asymptomatic vertebral fractures in patients with accentuated thoracic kyphosis or loss of height, or in whom bone density measurement is sufficiently low to make antiresorptive treatment highly desirable, i.e. a T-score below -2.5 (Figure 2).

Secondary causes of osteoporosis

Secondary causes of accelerated bone loss should be excluded when suggestive symptoms or signs of a secondary process are present, BMD is low relative to age- and weight-matched controls, or BMD declines at a greater rate than expected for age or fails to respond to appropriate therapy.

There are many medical conditions associated with osteoporosis (Table 2). Many of these present before osteoporosis develops, and knowledge of these pre-existing conditions may simply influence the decisions about whether to test for osteoporosis and then treat it. Routine screening of otherwise asymptomatic osteoporotic patients for these conditions is unnecessary. However, several secondary causes of accelerated bone loss are noteworthy because they may be silent and specific treatment of the condition may improve bone strength. The approximate prevalences of these conditions in osteoporotic populations are 30

to 40% for vitamin D deficiency, 16% for male hypogonadism, 4% for hyperthyroidism, 3% for coeliac disease, 1% for primary hyperparathyroidism and less than 1% for multiple myeloma.⁷⁻¹⁰

Patients with secondary causes of osteoporosis (other than vitamin D deficiency) should generally be referred to a specialist (Table 3).

General lifestyle measures for prevention

Lifestyle measures are generally recommended as the mainstay of osteoporosis prevention, although there is limited evidence to show that they improve peak bone mass or reduce fracture risk (see box on page 20).¹¹

Calcium supplements are advised for those who are unwilling or unable to meet the recommended dietary calcium intake. Vitamin D (ergocalciferol) supplements should be added in the presence of low vitamin D levels, that is, serum 25-hydroxyvitamin D below 42 nmol/L, although some evidence suggests that

serum vitamin D levels should be maintained above 50 nmol/L in those with or at risk for osteoporosis.^{12,13} Nursing home patients and others with poor sun exposure (including religious veiling) are at particular risk for vitamin D insufficiency. However, several recent Australian studies have shown that hypovitaminosis D is more widespread than previously thought.^{14,15}

Weight-bearing exercise has been shown in some studies to improve BMD or prevent its age-related decline. It is still unclear whether structured exercise programs are better than regular walking in this regard.

Smoking is associated with up to a twofold increased risk of hip fracture, although the effects of smoking cessation on BMD are not well documented. Similarly, excess alcohol and caffeine intake are known to be associated with lower bone mass, although benefits from cessation are likely to be associated with primary rather than secondary prevention of osteoporosis.

Treatment threshold

Although it is increasingly appreciated that osteoporosis is a major individual and public health burden, the place of new effective therapies is still being defined. Recent evidence demonstrates that newer potent antiresorptive therapies (see below) are effective in preventing up to 50% of recurrent fractures.¹⁶ Thus, for the patient with existing fracture, a decision to treat is usually straightforward.

If fracture has not yet occurred, treatment decisions should be based on the severity of the osteopenia and the presence of other risk factors including age, sex, family history and risk of falls. The use of hormone replacement therapy (HRT) to prevent menopause-related decline in BMD should be discussed with postmenopausal women in whom it is not otherwise contraindicated. The relation between breast cancer and HRT remains controversial, but it is often a

limiting factor in the minds of many women and their treating physicians.

In women reluctant or unable to take HRT, and in men, the place of other antiresorptive therapy in the management of asymptomatic osteopenia/osteoporosis is less clear, since the absolute risk reduction achievable within three to five years is generally smaller (50 patients need to be treated to reduce fractures by one).¹⁶ Nevertheless, the lifetime risk of fracture in men and women with osteoporosis may be substantial and a decision to treat will depend on the BMD, the presence of other risk factors (particularly older age), the patient's acceptance of treatment, and the potential side effects of many years of medication. Consideration of gender may be important because the rise in fracture incidence in men is delayed by about five to 10 years compared with women, although morbidity and mortality from fracture may be higher in men.²

Choice of treatment

All currently available approved therapies for osteoporosis inhibit bone resorption, which slows the rate of bone turnover and allows remineralisation of previously resorbed areas. This is the presumed basis for improvements in BMD seen with these therapies, and may also explain why increases in BMD plateau after several years of treatment.⁴

Oral bisphosphonates

Oral bisphosphonates directly inhibit osteoclast-mediated bone resorption. Alendronate (Fosamax) and risedronate (Actonel) are both potent oral bisphosphonates that have been shown in multiple randomised controlled trials to improve BMD and reduce the incidence of vertebral and nonvertebral fractures in women with osteoporosis.¹⁶ Both alendronate and risedronate are available on the PBS for the treatment of established osteoporosis in patients with fracture due to minimal trauma. Alendronate is also

Table 2. Secondary causes of osteoporosis

Conditions that may be 'silent' in association with osteoporosis

Screening for these diseases in selected osteoporotic patients may be important as specific therapy improves bone strength in addition to ameliorating other disease manifestations.

- Primary hyperparathyroidism (screening: calcium, parathyroid hormone)
- Hyperthyroidism (screening: thyroid stimulating hormone)
- Low vitamin D (screening: 25-hydroxyvitamin D)
- Coeliac disease (screening: endomysial antibodies)
- Myeloma (screening: serum and urinary immunoelectrophoretograms)
- Hypogonadism in men (screening: testosterone, luteinising hormone)

Conditions that usually present before osteoporosis develops

Patients in this category may warrant earlier investigation and/or treatment for osteoporosis. Routine screening for these conditions in asymptomatic osteoporotic patients is usually unnecessary.

- Cushing's disease
- Rheumatoid arthritis
- Ankylosing spondylitis
- Crohn's disease
- Chronic liver disease
- Chronic renal disease
- HIV infection

Drug therapies

Patients in this category may warrant earlier investigation and/or treatment for osteoporosis. Dose modification (or cessation if possible) may improve BMD.

- Glucocorticoid therapy (more than 7.5 mg prednisone daily or equivalent for longer than six months)
- Antiepileptic drugs (e.g. phenytoin)
- Possibly inhaled corticosteroids

Prevention of osteoporotic fracture

In general, osteoporotic fracture occurs when minimal trauma is applied to a bone with reduced strength (e.g. during a fall). Accordingly, strategies aimed at preventing falls or improving bone strength should reduce the risk of fracture.

Prevent falls

- Avoid sedative drugs
- Participate in weight-bearing exercise
- Use walking aids
- Use visual aids
- Modify environment

Improve bone strength

Prevent osteoporosis

- Ensure adequate nutrition, particularly calcium and vitamin D
- Participate in weight-bearing exercise

Treat osteoporosis

- Bisphosphonates
- Selective oestrogen receptor modulators
- Hormone replacement therapy
- Calcium plus vitamin D

there is some fracture prevention data available. It may still have a role in those patients who are intolerant to newer bisphosphonates.¹⁶ It is available on the PBS for the treatment of established osteoporosis in patients with fracture due to minimal trauma.

Selective oestrogen receptor modulators

Selective oestrogen receptor modulators (SERMs) act in a manner that is oestrogen-like in some tissues (bone and haematological tissue) but antioestrogenic in others (breast and uterus). The first SERM available, tamoxifen, has become well known for its role in the treatment of breast cancer.

Raloxifene (Evista) was developed as a bone-specific SERM, and has been shown to improve BMD and reduce the risk of vertebral fractures in patients with osteoporosis.¹⁷ Its efficacy in reducing the risk of nonvertebral fractures is, however, unclear. The use of raloxifene was associated with a reduced incidence of breast cancer in one clinical trial; further studies are in progress to clarify its potential use in women with increased breast cancer risk. Raloxifene may provoke or worsen hot flashes, and there is a small risk of venous thromboembolism (comparable to that seen with HRT) so it should not, therefore, be used in women with a prior history of thromboembolic disorders. It is also contraindicated in premenopausal women and in men. It is available on the PBS for the treatment of established osteoporosis in postmenopausal women with fracture due to minimal trauma.

Curiously, the observed reduction in fracture rates with both oral bisphosphonates and SERMs exceeds that expected from their effect on BMD, raising the possibility that they affect 'bone quality' in a manner which is only partially explained by increased mineral content. As fracture prevention is the primary goal of osteoporosis treatment, drugs with proven antifracture efficacy are more

Table 3. Considerations for specialist referral

- Complex co-existing medical conditions
- Secondary causes of osteoporosis
- No improvement in BMD after therapy
- Recurrent fracture despite therapy

reimbursed for the treatment of established osteoporosis in men.

These medications also improve BMD in patients with osteopenia, although study sizes and duration have not yet

been adequate to detect significant fracture prevention in this group.

Alendronate and risedronate have been associated with oesophagitis although in several large studies the occurrence of gastrointestinal symptoms was similar to that seen with placebo.¹⁶ Nevertheless, symptoms are more common in those with pre-existing dyspeptic disorders, and achalasia and oesophageal stricture are absolute contradictions to their use.

Disodium etidronate (Didronel, Didrocal) is a less potent first-generation oral bisphosphonate that gives smaller improvements in BMD and for which

strongly recommended than drugs for which BMD improvement is used as a measure of efficacy.

Hormone replacement therapy

HRT in women has been known for many years to ameliorate menopausal bone loss, and has been the mainstay of osteoporosis prevention in postmenopausal women. However, firm evidence that HRT reduces fracture incidence is less forthcoming and there has been increasing patient concern about the side effects (particularly the small excess breast cancer risk) observed with long term use.¹⁸ HRT undoubtedly still has an important role in women for whom other menopausal symptoms respond to oestrogen replacement, despite some doubt about its value in treating established osteoporosis.

Tibolone (Livial) is a promising therapy in osteoporosis prevention and deserves further study. Similarly, the use of testosterone in hypogonadal men with low bone mass has been shown to improve BMD, although there are no data on fracture prevention with long term use of androgen therapy. Also, there is little evidence to support the use of androgenic steroids to reduce fracture risk in eugonadal men or women with osteoporosis. Phytoestrogens such as Promensil and Rimostil have been popular alternatives as 'natural' remedies but neither can currently be recommended as treatment for osteoporosis.

Calcitriol

The use of calcitriol (1,25-dihydroxyvitamin D₃ [Citrihexal, Kosteol, Rocaltrol, Sitriol]) in osteoporosis management has largely been superseded by the more potent antiresorptive therapies discussed above, although there may still be a place for this drug in selected instances. A recent study demonstrated that the use of calcitriol in combination with HRT had an additive benefit on BMD.¹⁹ The potential use of other combination therapies needs further study. Calcitriol is

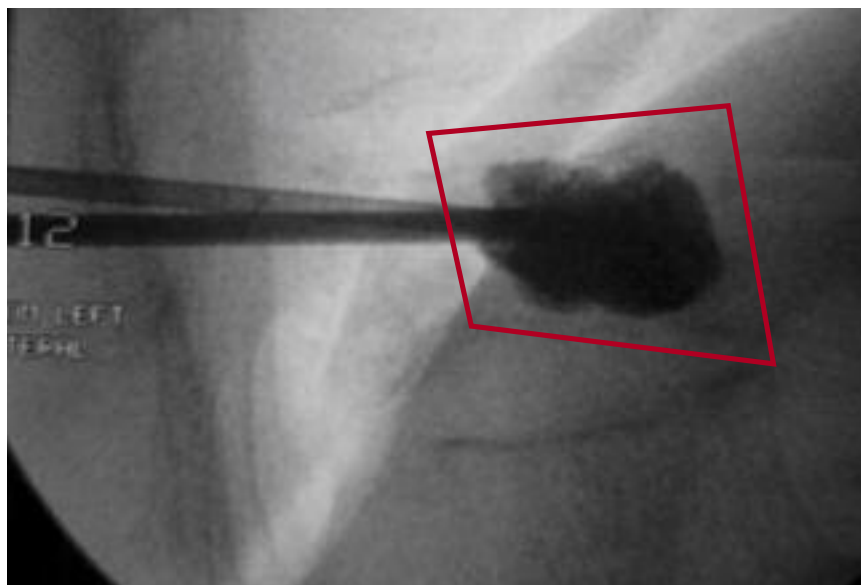


Figure 3. Vertebroplasty. Polymethylmethacrylate cement is injected via an 11-gauge needle into a vertebral crush fracture (outlined in red) under fluoroscopic guidance.

Consultant's comment

Osteoporosis is set to become a major global public health problem of this century. In 2001, nearly two million Australians have osteoporosis, and three-quarters of these are women. If nothing is done to prevent the condition and identify and treat those at risk, this will increase to three million people by 2021, with a fragility fracture occurring every three minutes. Between 1991 and 2031, it is anticipated that hip fracture rates in Australia will treble. The past decade has witnessed an explosion in our knowledge of basic bone cell biology and has provided an understanding of the mechanisms of action of the drugs used to treat osteoporosis.

Now that effective treatments are available, the challenge for all doctors – and GPs in particular – is to identify those who would benefit most from treatment. Patients with a prior fragility fracture would certainly benefit the most; however, the majority of these patients are not yet being treated. Clearly there needs to be a greater awareness among their primary carers that the first fracture may herald many more unless assessment and treatment are initiated. In patients without a fracture the decision regarding when to treat is less clear, but it would seem sensible to consider other risk factors, such as age, that would confer a similar degree of risk to the presence of a fragility fracture.

This article by Dr Clifton-Bligh and Professor Sambrook is timely and also emphasises the importance of adequate calcium and vitamin D nutrition and exercise as adjuncts in the prevention and treatment of this potentially crippling disease.

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available on the PBS for the treatment of established osteoporosis in patients with fracture due to minimal trauma.

Vertebroplasty for fracture treatment

Pain associated with a vertebral fracture is often severe, and indirect costs associated with prolonged immobility may be considerable (for example, adverse health outcomes, inability to work and need for ancillary care). A recent advance in the treatment of existing fracture, vertebroplasty is a technique for relieving pain in vertebral compression fractures by percutaneous injection of polymethylmethacrylate bone cement under fluoroscopic guidance (Figure 3).²⁰ Originally used as a treatment for malignant vertebral fracture and vertebral haemangioma, there has been wider application to include osteoporotic fractures in those with severe pain that is unresponsive to narcotic analgesia.

The response to vertebroplasty is often dramatic, with many patients reducing or discontinuing analgesic medications and up to one-third immediately returning to full activity. Same-day discharge is usually feasible, and the reported complication rate is low. However, possible complications include spinal cord compression (1% of patients treated), which may require orthopaedic decompression and may, albeit rarely, result in permanent disability. Judicious referral is therefore needed, with careful consideration of the risk–benefit ratio.

Looking to the future

Management of osteoporosis is a challenge requiring greater awareness in the medical profession as well as in the community, and wider use of effective treatments for those who have already sustained a fracture. Data on fracture risk reduction associated with long term use of bisphosphonates and SERMs will become available, allowing for rational treatment decisions in those with osteopenia. New therapies that may become

available are antiresorptive agents such as calcitonin and, possibly, proformative agents such as parathyroid hormone.

Nasal calcitonin, although not yet available in Australia and having comparatively minor effects on BMD compared with bisphosphonates and hormonal therapy, may have a role in patients who develop side effects or are unresponsive to these medications.²¹ Combination therapy is also receiving attention in ongoing studies, and it is possible that antiresorptive drugs of different classes may have additive benefits (for example, bisphosphonates plus HRT, SERM or calcitonin). Parathyroid hormone given by subcutaneous injection has been shown to have considerable anabolic properties on BMD and markers of bone turnover, and may become available in the future.²²

Simple preventive strategies, however, continue to be underutilised, and a fitter elderly population with higher individual BMD could potentially reduce the incidence of morbidity due to osteoporosis.

An expensive disease

Osteoporosis is an expensive disease in relative terms. The direct health costs for the 1.9 million women in Australia who have the condition in 2001 are estimated to be \$1.9 billion per annum, with a heavy burden on hospitals and nursing homes.²³ With the numbers of fractures increasing by 4% each year, osteoporosis will become increasingly costly, both in terms of health costs and indirect costs such as lost earnings, volunteer carers, modifications and equipment.²³

Osteoporosis, arthritis and other bone conditions are becoming a huge burden in all countries as populations age and countries experience greater life expectancy. To highlight the growing problem of these diseases around the world the United Nations has endorsed the decade 2000 to 2010 as the 'Bone and Joint Decade'. **MT**

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

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