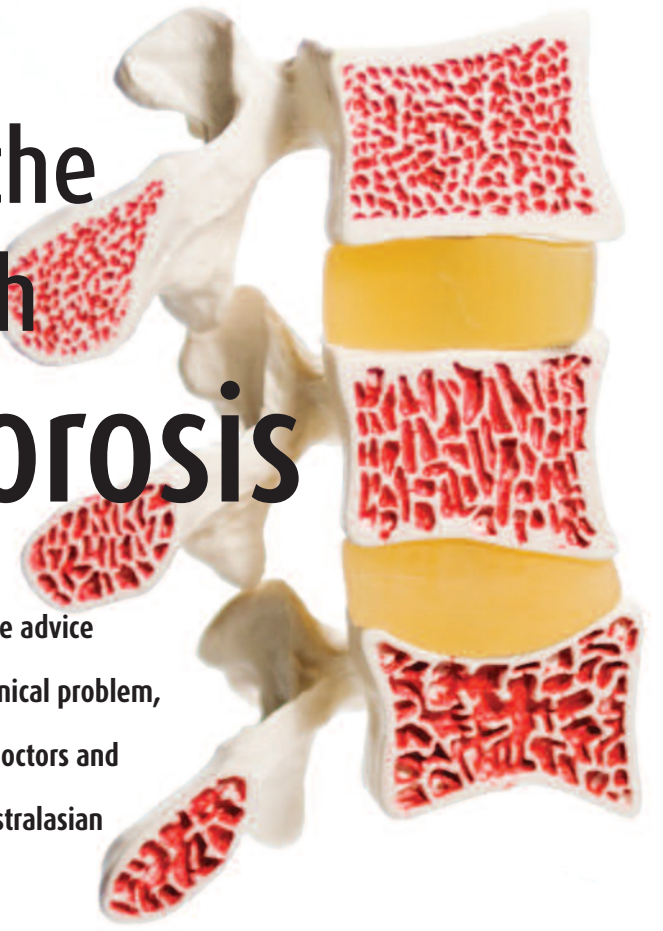
Managing the patient with osteoporosis



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In this series we present authoritative advice on the investigation of a common clinical problem, especially commissioned for family doctors and written by members of the Royal Australasian College of Physicians.

Osteoporosis is a common and treatable condition. Among women, it is more common than myocardial infarcts, strokes and breast cancer combined. Despite there being a range of mostly well-tolerated and effective treatment options, it is an underdiagnosed and undertreated condition.

Osteoporosis is a systemic metabolic disease in which a decrease in bone mass as well as deterioration of skeletal architecture weakens the skeleton, predisposing the bones to an increased risk of fracture. The burden of osteoporotic fractures is significant and the health costs involved are often underappreciated. In Australia, one in two women and one in three men over 60 years of age will sustain an osteoporotic fracture in their remaining lifetime.[1] This will cost us more than $1.9 billion a year in direct health costs, with total direct and indirect costs estimated at more than $7 billion annually, which is about $1 million per hour.[2] Moreover, with the ageing of the population, these figures are estimated to increase significantly over the next few decades.

Clinical presentation

Osteoporosis is a silent disease until a fracture occurs. The most common sites of osteoporotic

IN SUMMARY

- **Osteoporosis is a common condition and osteoporotic fractures lead to significant morbidity and premature mortality.**
- **There are excellent diagnostic tools and many treatment options available for patients diagnosed with osteoporosis.**
- **Most (70 to 95%) patients with minimal trauma fractures who are treated at Australian hospitals are neither investigated nor treated for osteoporosis. Lack of awareness among both treating clinicians and patients is likely to be a major contributing factor.**
- **GPs can play an important role in the recognition of the condition and its subsequent management, in consultation with an endocrinologist or rheumatologist if required.**

ILLUSTRATION: MODEL SHOWING PROGRESSIVE LOSS OF BONE DENSITY IN OSTEOPOROSIS.

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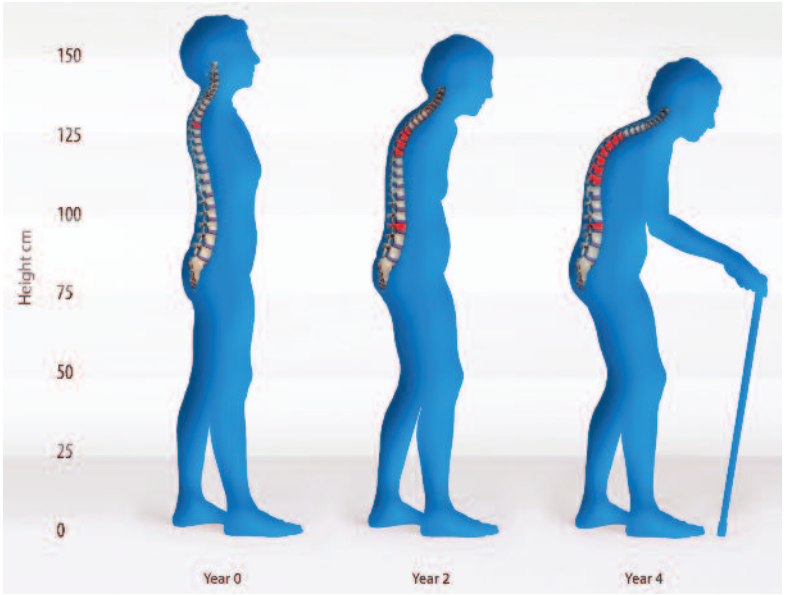

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Figure 1. Loss of height associated with increasing severity of osteoporosis.

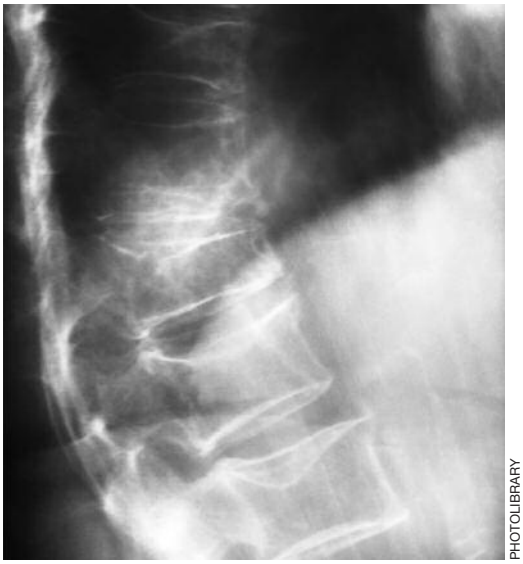

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Figure 2. Lateral thoracic x-ray showing a vertebral 'wedge' fracture.

Table 1. Risk factors for osteoporosis

Nonmodifiable

- Age
- Genetics and family history
- Previous minimal trauma fractures
- Chronic diseases such as chronic renal failure and malabsorptive syndromes

Modifiable

- Oestrogen deficiency in women, including postmenopause
- Testosterone deficiency in men
- Ongoing corticosteroid use (depending on dose)
- Uncontrolled hyperthyroidism
- Hyperparathyroidism
- Coeliac disease
- Multiple myeloma
- Smoking
- Heavy alcohol intake
- Lack of weight-bearing exercise
- Low-calcium diet
- Limited sunshine exposure
- Low body weight

fractures are the spine, hip and wrist but virtually any bone can and does fracture as part of the bone fragility state. Both modifiable and nonmodifiable factors contribute to bone fragility (Table 1).

Clinical presentation varies according to the site of fracture. Spinal fractures are often asymptomatic (about 75% are not clinically recognised) and can lead to a progressive loss of height (Figure 1). Comparing a patient's current height to their young adult height by asking them or checking height measurements on an old passport can be useful. In our experience, recall bias seems not to be a problem as most people remember their peak adult height, often in old imperial units. Spinal radiography showing classical 'wedge' or crush fractures is diagnostic of osteoporosis (Figure 2).

Hip and wrist osteoporotic fractures are most common in the context of minimal trauma (an arbitrary amount of trauma that is deemed not likely to cause normal bone to fracture). It is important that all fractures following minimal trauma be considered indicative of osteoporosis unless proven otherwise.

Investigations

A diagnosis of osteoporosis is made in the presence of fragility fracture history and/or evaluation of bone densitometry. Blood and urine tests are used in patients with osteoporosis to screen for secondary causes and to monitor bone turnover (Table 2).

An approach to managing a patient with the condition is provided in the flowchart on page 51.

Bone density measurement

Measurement of bone mineral density (BMD) with dual energy x-ray absorptiometry (DXA) is a quick, noninvasive means of estimating bone strength. It takes around 10 minutes and involves the patient lying in a DXA machine as measurements are taken of the spine and hips (Figure 3). If there is no fracture then a diagnosis of osteoporosis can be made on bone density criteria. Bone densitometry is not needed to make the diagnosis of osteoporosis if the individual has suffered a fragility fracture. However, it is helpful in deciding further management and following a patient, as indicated in the flowchart.

Table 2. Blood and urine tests for osteoporosis

Screening tests for secondary causes

- Serum corrected calcium level – to identify hyper- or hypocalcaemia
- Serum 25-hydroxyvitamin D – for vitamin D deficiency or insufficiency
- Parathyroid hormone – to exclude primary hyperparathyroidism
- Thyroid function tests (i.e. thyroid stimulating hormone) – for hyperthyroidism
- Serum protein electrophoresis – for multiple myeloma
- Antigliadin and anti-tissue transglutaminase antibodies – for coeliac disease

Bone turnover markers

- Bone formation markers – serum osteocalcin, bone-specific alkaline phosphatase, propeptide of type I procollagen (PINP)
- Bone resorption markers – serum C-telopeptide crosslinked type 1 collagen (CTX), urine hydroxyproline/creatinine ratio, urine N-telopeptide crosslinked type I collagen (NTX)/creatinine ratio, urine deoxypyridinoline (DPD)/creatinine ratio

The criteria for diagnosis of osteoporosis are based on the patient's T-score. This is a value that compares the patient's values to those of young, healthy individuals in units of standard deviations. A T-score above -1 is deemed normal, a score between -1 and above -2.5 is defined as osteopenia and a score of -2.5 or below is defined as osteoporosis. In Australia, the Geelong database values should be used for normal comparisons.

Bone mineral densitometry also provides a Z-score. This compares the patient's values to those of other people of the same sex, age and, depending on the type of instrument used, weight. It is important to remember that Z-scores are not used for diagnosing osteoporosis. However, disproportionately low scores (below -2.0) may be an indication of the presence of a secondary cause of osteoporosis, such as coeliac disease, hyperparathyroidism or thyrotoxicosis.

Monitoring of progress of disease and response to treatment can also be performed by serial bone density measurements. These should be made on the same DXA machine as changes with treatment are modest, the error of measurement is significant and there is considerable variation between different machines. To complicate matters further, there are different DXA systems available, predominantly GE-LUNAR, Norland and Hologic, and comparisons between raw BMD scores are not valid across machines. Comparing the T-scores is more meaningful although still not ideal as the reference populations used by the manufacturers are different.

Management

Decisions about treatment for a patient with osteoporosis may be enhanced by an estimate of absolute fracture risk, such as the Australian-derived Garvan–Dubbo Fracture Risk Calculator (http://www.fracturerisk calculator.com) and the WHO-developed FRAX calculator from Sheffield, UK (http://www.sheffield.ac.uk/FRAX).

The Fracture Risk Calculator, developed using data from the Dubbo Osteoporosis Epidemiology Study conducted by the Garvan Institute of Medical Research, Sydney, uses age, sex, prior fracture history, falls history and bone density to estimate five- and 10-year absolute risks of hip and nonhip fragility fractures. This information can help decisions about therapy and may enhance adherence.

Management of patients with osteoporosis includes advocating a healthy lifestyle and using specific pharmacological therapies.

PHOTOLIBRARY

Figure 3. Bone density measurement by dual energy x-ray absorptiometry (DXA).

Lifestyle factors

Calcium

An adequate calcium intake is considered a sensible health policy but evidence for specific fracture risk benefit is limited. As all current effective pharmacotherapy for osteoporosis has been evaluated in the presence of adequate calcium intakes and adequate vitamin D serum levels, adequate intakes of calcium (and also adequate serum vitamin D levels) should be ensured.

A person's intake of dietary calcium should be checked, the recommended daily intake being three to four serves of calcium. Foods rich in calcium include dairy products such as milk, yoghurt and cheese as well as nuts, sardines and leafy vegetables such as spinach. One serve of calcium is defined as one glass of milk (200 to 250 mL), one tub of yoghurt (200 g) or one slice of cheese (about 30 g).

If people are unable to obtain adequate calcium through their diet, supplementation with over-the-counter calcium preparations is recommended. Ideally these should taken with a meal.

There has lately been concern about the safety of calcium supplements, with a recent meta-analysis suggesting a small increase in myocardial infarct risk with calcium supplementation.[3] However, in the meta-analysis there was no significant increased risk of cerebrovascular events or death risk. In these studies, large doses of calcium supplements were used on

An approach to investigating a patient with osteoporosis

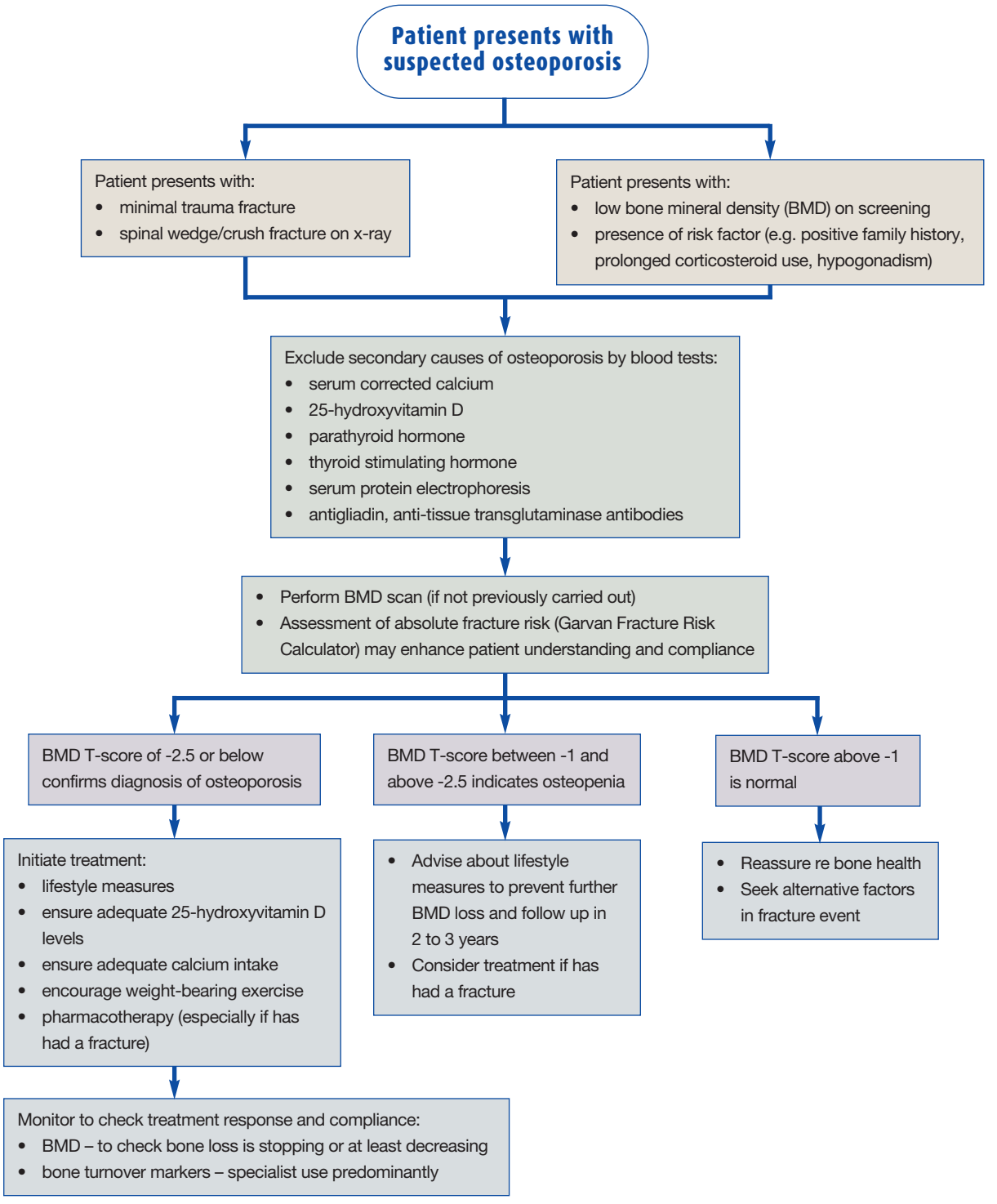

Table 3. Pharmacological therapies

Antiresorptive therapies
- Bisphosphonates
- Raloxifene
- Tibolone
- Hormone replacement therapy

Dual acting agent
- Strontium ranelate

Anabolic therapy
- Teriparatide

top of generally good dietary calcium intakes. It would seem prudent to advise total (i.e. dietary and supplemental) calcium intakes of about 1200 mg daily and to encourage patients to take any supplements with food to slow absorption.

Vitamin D

An adequate vitamin D level is also considered a sensible health policy but evidence for specific fracture risk benefit is limited. As mentioned for calcium above, all the effective pharmacotherapy for osteoporosis has been evaluated in the presence of adequate intakes of calcium and adequate serum levels of vitamin D so adequate vitamin D serum concentrations should be ensured.

Low vitamin D levels are common even in otherwise healthy individuals. The main source of vitamin D is its formation in the skin through exposure to ultraviolet light; the intake from dietary sources is minimal. The recommended skin exposure is five to 15 minutes of sunlight four to six times a week but avoiding the hours between 10 a.m. and 2 p.m. Avoidance of the most dangerous ultraviolet exposure in the middle of the day is appropriate, especially in summer, with responsible use of ultraviolet blocking agents. The length of exposure required is greater in dark-skinned people. Groups particularly at risk of vitamin D deficiency are institutionalised patients and those who expose minimal skin areas (e.g. for cultural reasons).

Checking for deficiency requires the performing of a simple serum test for 25-hydroxyvitamin D (25-OHD). The target range of 25-OHD remains controversial with values ranging between 50 and 110 nmol/L being variously recommended for optimal bone health. Supplementation with over-the-counter preparations of vitamin D_3 (cholecalciferol) often requires 1000 to 2000 IU cholecalciferol daily to be effective. Rechecking serum 25-OHD levels after a few months can ascertain adequacy.

Exercise

Weight-bearing exercise such as walking and running is more effective than exercise that is not weight bearing in maintaining bone density. Patients should be encouraged to walk at least 30 minutes on at least five days of every week. There is limited evidence that exercise translates to reduced fracture risk but some evidence that it modestly improves bone density. Similarly, falls risk reduction strategies such as Tai Chi can reduce injurious falls but there is limited evidence that they actually reduce fracture risk.

Cessation of smoking and reduction in alcohol intake

Stopping smoking and reducing intake of alcohol are recommended as part of a healthy lifestyle. There is some evidence of benefit on bone health as well.

Pharmacotherapy

Pharmacological therapies for osteoporosis are classified as antiresorptive, dual-acting and anabolic, as shown in Table 3.

Bisphosphonates

Bisphosphonates remain the mainstay of treatment in patients with osteoporosis. They have been shown in women and men to reduce the risk of vertebral fracture and hip fracture by 40 to 60%, and of other fragility fractures by about 30%.[4-6]

There are two potent oral bisphosphonates on the market in Australia, alendronate and risedronate. Both of these are available as once-weekly preparations, and risedronate is also available as a once-monthly preparation that is as efficacious as the weekly tablets and has the advantage of less frequent administration to enhance compliance. Both are also available in combination packs that provide extra vitamin D (alone or with the bisphosphonate) and with calcium to be taken distant in time from the bisphosphonate. (Taking a bisphosphonate with food or mineral-rich liquids or other tablets effectively reduces their absorption to zero.)

Bisphosphonates target bone resorption, which is usually elevated in osteoporosis. Compliance is a major consideration with bisphosphonates in particular, given their poor absorption and thus strict dosing requirements. It is crucial that patients are specifically reminded to take the medication first thing in the morning on an empty stomach with a full glass of water. They must not consume any food, beverage or other medications before or with it and they must then wait for at least 30 minutes before eating. It is also important to stress that they remain upright (i.e. not go back to bed) after taking a bisphosphonate, to reduce the risk of oesophageal irritation from the medication associated with gastro-oesophageal reflux.

An intravenous bisphosphonate is also available – zoledronic acid. This is especially suitable for patients who are unable to tolerate oral bisphosphonates or are nonadherent to treatment. Zoledronic acid has been shown in trials to be at least as effective, if not more effective, than oral bisphosphonates. It is approved to be given as a once-yearly infusion but its action can be very long-lasting (as measured by continued suppression of bone turnover markers), and some individuals

seem not to require repeat dosing for two to three years.[7]

The rare complication of osteonecrosis of the jaw has been reported, leading to much concern among clinicians and patients alike. This is a rare and serious condition of largely unknown aetiology. It is important to stress that most case reports are usually in the context of bisphosphonates used in cancer patients, where much larger or more frequent dosing regimens are used than in patients with osteoporosis. Nevertheless, it is prudent to ask patients if they have any dental extractions or implants planned because bisphosphonate treatment could be either delayed until these are completed and the wounds healed or stopped for some months around these procedures.

Current Pharmaceutical Benefit Scheme (PBS) indications for alendronate (10 mg daily or 70 mg once weekly), risesdronate (5 mg daily or 35 mg once weekly) and zoledronic acid (5 mg once yearly) are:

- treatment as the sole PBS-subsidised antiresorptive agent for osteoporosis in patients aged 70 years and older with a BMD T-score of -3.0 or less
- treatment as the sole PBS-subsidised antiresorptive agent for established osteoporosis in patients with fracture due to minimal trauma.

Risedronate and zoledronic acid are also PBS-listed as treatment as the sole PBS-subsidised antiresorptive agent for corticosteroid-induced osteoporosis in patients on long-term high-dose corticosteroid therapy. The PBS subsidy for zoledronic acid for osteoporosis is currently limited to one osteoporosis-related treatment each year for three years.

Raloxifene

Raloxifene, a selective oestrogen receptor modulator (SERM), simulates the action of oestrogen on bone and inhibits bone resorption. Through its antioestrogenic effect on breast tissue, this oral medication has the additional benefit of preventing hormone dependent breast cancers.

Raloxifene reduces the risk of vertebral fractures predominantly; there is limited evidence for any nonvertebral fracture reduction. It appears to be neutral with respect to cardiovascular and cerebrovascular risks but can exacerbate menopausal symptoms in perimenopausal women, particularly hot flushes.[10] Like oestrogens, it also increases the risk of venous thromboses.

Raloxifene is listed on the PBS for treatment as the sole PBS-subsidised antiresorptive agent for established postmenopausal osteoporosis in patients with fracture due to minimal trauma.

Tibolone

Tibolone, a selective tissue oestrogenic activity regulator (STEAR), is similar to raloxifene in having a pro-oestrogenic effect on bone but, unlike raloxifene, it reduces menopausal symptoms. It reduces the risk of both vertebral and nonvertebral fractures, and it also reduces the risk of invasive breast and colon cancer.[9] One study has shown its use was associated with a small increase in strokes in women older than 70 years, and tibolone should be used with caution in this age group.[11]

Tibolone is approved by the Therapeutic Goods Administration for the short-term treatment of symptoms resulting from the natural or surgical menopause in postmenopausal women, and as second-line therapy for the prevention of BMD loss in postmenopausal women at high risk of future osteoporotic fractures who are intolerant of, or contraindicated for, other medications approved for BMD loss. It is, however, not PBS-listed for these indications.

Hormone replacement therapy

Oestrogen therapy can prevent bone loss in postmenopausal women and reduce fracture risk. This benefit has been shown in women selected for being postmenopausal without any prior osteoporosis diagnosis. However, because HRT has been associated with a small relative increase in the incidence of cardiovascular disease and breast cancer in the Women's Health Initiative Study, it is not recommended for management of fracture risk alone. HRT is indicated for the short-term relief of menopausal symptoms and has the additional benefit of preventing bone loss in these women.

Strontium ranelate

Strontium ranelate is promoted as a dual-acting bone agent, having both anabolic and antiresorptive properties. However, the mechanism and site of these effects is not entirely clear. Nevertheless, it has been shown to have both vertebral and nonvertebral fracture risk reduction effects

Useful internet sites for osteoporosis information

- Osteoporosis Australia – http://www.osteoporosis.org.au
- The Royal Australian College of General Practitioners – http://www.racgp.org.au Specifically, the NHMRC-endorsed guideline, *Clinical Guideline for the Prevention and Treatment of Osteoporosis in Postmenopausal Women and Older Men*, can be downloaded (http://www.racgp.org.au/Content/NavigationMenu/ClinicalResources/RACGPGuidelines/osteoporosis1/RACGP_Osteo_guideline.pdf)
- Australian and New Zealand Bone and Mineral Society – http://www.anzbms.org.au
- The American Society for Bone and Mineral Research – http://www.asbmr.org
- International Bone and Mineral Society – http://www.ibmsonline.org

Consultant's comment

Why should GPs consider a diagnosis of osteoporosis when reviewing a patient? Firstly, because it is common, affecting one in two women and one in three to four men over the age of 60 years; secondly, because it is largely preventable; and thirdly, because it is expensive, costing Australians over $1.9 billion a year in direct health costs with total, direct and indirect costs estimated at over $7 billion annually. In addition, there have been recent advances in determining absolute fracture risk, akin to longstanding cardiovascular risk calculators. These fracture risk calculators are useful in helping to decide which patients require pharmacological intervention with antiosteoporosis drugs. Such drugs are very effective, reducing fractures by 50 to 70%, and an increased choice of medications, with differing benefit/risk profiles, is now available.

The array of medications may lead to uncertainty in prescribing for general practitioners. To overcome this potential for confusion, the NHMRC-endorsed guideline for the management of osteoporosis – *Clinical Guideline for the Prevention and Treatment of Osteoporosis in Postmenopausal Women and Older Men* – has recently been published by the Royal Australian College of General Practitioners. (This guideline can be downloaded from the RACGP website: http://www.racgp.org.au/guidelines/musculoskeletaldiseases/osteoporosis.)

This review of osteoporosis investigation and management by Dr Devina Joshi and colleagues is therefore timely and may help to reduce the evidence–practice gap in osteoporosis, which is one of the largest existing in medicine today.

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of a similar magnitude to the bisphosphonates.[8,9]

Strontium ranelate is given as a once daily oral dose (as a powder mixed with water) and is best taken at bedtime, at least two hours after food. Possible side effects include nausea, diarrhoea, headache and skin irritation. An uncommon side effect is venous thrombosis and because of this the medication should be avoided in patients with a past history of or risk factors for thrombosis.

Strontium ranelate is listed on the PBS for use as the sole PBS-subsidised antiresorptive agent for osteoporosis in women aged 70 years and older with a BMD T-score of -3.0 or less, and as the sole PBS-subsidised antiresorptive agent for established postmenopausal osteoporosis in patients with fracture due to minimal trauma.

Teriparatide

Recombinant human parathyroid hormone 1–34 (teriparatide) is an anabolic agent that reduces vertebral fracture risk by 65% and nonvertebral fracture risk by 53%.[12] It is administered by subcutaneous injection and can be used for a total of 18 months only, as the pivotal studies were stopped at about that time because of reports of osteosarcoma in animal toxicity studies. There is no evidence of an increased risk of osteosarcoma in individuals using it for osteoporosis therapy. Side effects include dizziness and leg cramps.

Teriparatide is listed on the PBS for use as the sole PBS-subsidised antiresorptive agent in patients with a BMD T-score of -3.0 or less who have had at least two minimal trauma fractures, at least one of which had to have been while they were on treatment with antiresorptive therapy at adequate doses.

Timing and duration of treatment

It is never too late to start treatment for osteoporosis because the aim of treatment is to stop further bone loss. Objective benefits can be seen in the form of increases in BMD scores (usually within a year), decreases in bone turnover markers (usually within three to six months) and, most importantly, reduction in fracture risk (within six to 12 months).

Old age *per se* is not a risk factor for a patient developing complications while taking antiosteoporotic medications. Bisphosphonates, strontium ranelate and teriparatide are all contraindicated in patients with severe renal impairment (estimated glomerular filtration rate less than 30 mL/min/1.73m^2).

The duration of optimal treatment needs to be individualised to the patient. In general terms, most people with established osteoporosis (i.e. a history of minimal trauma fractures or BMD T-score of -2.5 or less) require long-term treatment (longer than five years). Close monitoring is required during this time, using BMD measurement. In some situations, bone turnover markers can be useful to assess response to treatment and they can also help identify noncompliance. After this time, if the individual continues to have deterioration of BMD and/or new fractures, continuation or a change of therapy is warranted. If, on the other hand, the situation is stable and the osteoporosis not severe (e.g. BMD T-score above -3), temporary discontinuation of treatment is not unreasonable provided there is ongoing close monitoring at least annually.

Information sources

Patient information

Patients can be referred to the Osteoporosis Australia website (http://www.osteoporosis.org.au) for further information.

This site presents information in an

easy to understand format and has fact sheets and other resources that can be downloaded, some in several languages.

Information for general practitioners

The Royal College of General Practitioners (RACGP) publication *Clinical Guideline for the Prevention and Treatment of Osteoporosis in Postmenopausal Women and Older Men* can be downloaded from the RACGP website (http://www.racgp.org.au/guidelines/musculoskeletaldiseases/osteoporosis).

Further information on the diagnosis and management of osteoporosis can also be obtained at the Osteoporosis Australia website as well as the websites of the Australian and New Zealand, American and International Bone and Mineral Societies (see the box on page 55).

Rural general practice and osteoporosis management

Bone mineral densitometry is performed in most places that have nuclear medicine facilities and in many radiology practices. It is important that BMD is measured before treatment is started, to establish the diagnosis. However, a BMD above the 'osteoporosis' threshold of T-score -2.5 does not exclude osteoporosis as a contributory factor in a fragility fracture.

Bone density measurement can also be used for monitoring of progress once treatment is initiated, both to assess compliance and to provide feedback. Usually it only needs to be performed every one to two years. Financial compensation is available to patients from rural areas who travel long distances to have these tests performed.

Pharmacological treatment can be readily managed by rural GPs themselves or in a shared-care model with an endocrinologist or rheumatologist. Visits to such specialists may be at intervals of six to 12 months initially but at much longer intervals subsequently, if and as needed.

Conclusion

Osteoporosis is a common systemic disease that predisposes patients to fractures that usually have a significant impact on quality of life, health care costs and survival. The array of treatment modalities available means there is much to offer patients that can make significant differences to their lives and reduce the risk of future fractures. MT

References

1. Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA. Symptomatic fracture incidence in elderly men and women: the Dubbo Osteoporosis Epidemiology Study (DOES). Osteoporosis Int 1994; 4: 277-282.
2. Access Economics; commissioned by Osteoporosis Australia. The burden of brittle bones in Australia: costing osteoporosis in Australia. Canberra: Access Economics; 2001.
3. Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 2010; 341: c3691.
4. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995; 333: 1437-1443.
5. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with post - menopausal osteoporosis: a randomized con - trolled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999; 282: 1344-1352.
6. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med 2000; 343: 604-610.
7. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007; 356: 1809-1822.
8. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004; 350: 459-468.
9. Reginster JY, Seeman E, de Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005; 90: 2816-2822.
10. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999; 282: 637-645.
11. Cummings SR, Ettinger B, Delmas PD, et al. The effects of tibolone in older postmenopausal women. N Engl J Med 2008; 359: 697-708.
12. Hodsman AB, Bauer DC, Dempster DW, et al. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev 2005; 26: 688-703.

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