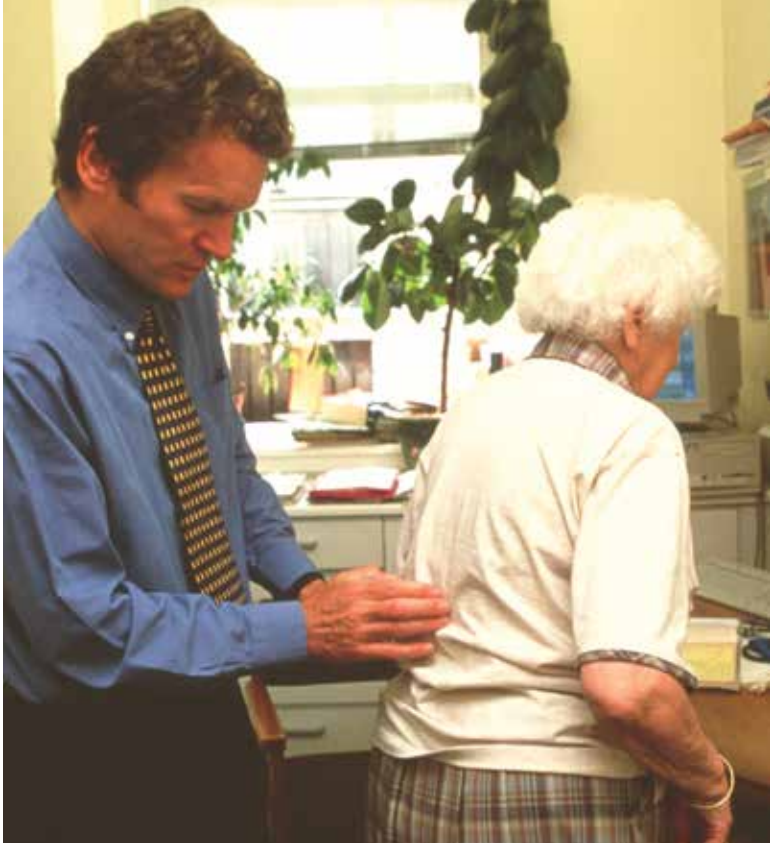
Osteoporosis in postmenopausal women

Key aspects of prevention and treatment



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Osteoporosis is a common and costly condition that has significant morbidity and mortality after a fracture. Despite robust evidence that treatment reduces the risk of future fractures, many people in Australia are not adequately treated. This review covers our current understanding of prevention and treatment of osteoporosis in postmenopausal women in Australia.

KEY POINTS

- All patients with osteoporosis should be reviewed with regard to modifiable factors and use of nonpharmacological therapies.
- Calcium supplementation is recommended for patients with low dietary calcium intake after discussion of the potential risks.
- Vitamin D supplementation is recommended to maintain vitamin D sufficiency.
- Antiresorptive therapies (bisphosphonates and denosumab) are highly effective in reducing vertebral, hip and nonvertebral fractures and have a safe adverse effect profile.
- Hormone-related therapies are a good alternative for women in the perimenopausal or early postmenopausal stages.
- Teriparatide is the only anabolic therapy currently available in Australia.

Osteoporosis is a systemic skeletal disorder characterised by reduction in bone mass and disruption of bone microarchitecture, leading to decreased bone strength and increased susceptibility to fragility fractures. Osteoporosis is a significant health issue, with 4.7 million people in Australia (66%) over 50 years of age affected by poor bone health. In 2012, the total cost of osteoporosis and osteopenia was $2.75 billion.[1]

The prevalence of osteoporosis and its associated costs are predicted to increase every year. Prevalence data are likely to provide a significant underestimate because the diagnosis is often missed until a fracture occurs. Furthermore, diagnostic investigations (primarily bone mineral density [BMD] testing) are underutilised even after a patient has a minimal trauma fracture. As a result, people with undiagnosed osteoporosis are at high risk of a fracture and its associated morbidity, mortality and financial costs. Screening and confirmatory dual-energy x-ray absorptiometry (DXA) should be used in people at risk, and after a fracture. Inadequate treatment of a first fracture constitutes a critical missed opportunity to prevent subsequent fractures.

As the population ages, the number of fractures in older adults will increase. These fracture rates can be reduced with an increase in diagnosis and treatment of osteoporosis and increased awareness of falls prevention.[2,3] Thus, early identification and treatment of patients at risk of osteoporosis and those with a fragility fracture may reduce the health burden and associated costs.

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Nonpharmacological prevention and treatment options

Exercise and other modifiable lifestyle factors

There is evidence that regular moderate-intensity exercise in children increases bone mineral content in weight-loading sites (femur, tibia and fibula) and may delay the onset of osteoporosis in later life.[4,5] In adults, a meta-analysis evaluating the effect of resistance exercise found an increase in the BMD at the femoral neck and lumbar spine only when resistance training was combined with high-impact or weight-bearing exercise (no significant effect was seen with resistance training alone).[6] Because fractures result from falls, exercise and balance programs have been evaluated for reducing fractures. A multimodal exercise program targeting prevention of functional decline through resistance training, education and behavioural change showed improvements in lumbar spine and femoral neck BMD, muscle strength and balance, but no change in falls rate.[7] There has been one randomised controlled trial with fracture as the primary outcome and three meta-analyses that suggest exercise reduces fractures if it includes resistance training or multimodal robust exercise regimens.[8-10] However, the effects of exercise are modest and site-specific. Exercises should be tailored to individuals and initiated under supervision. Exercises such as yoga and tai chi may improve balance and muscle tone and may reduce falls. Patients with low vertebral BMD or previous vertebral fractures should avoid forward spine flexion, and any targeted exercises should begin at low intensity with a gradual stepwise increase in intensity, repetitions and movement patterns to allow for dispersed load distribution.[11]

Other lifestyle factors that should be addressed include cigarette smoking (which is associated with low BMD), excessive alcohol consumption (which contributes to low BMD and increases falls and fracture risk) and assessment of balance, home environment and other medications (such as sedatives, antihypertensive medications and corticosteroids), all of which can contribute to excess falls and fractures.

Calcium

The current recommended daily intake of calcium is 1300 mg (three to four serves of dairy products) for postmenopausal women, ideally achieved through dietary means. Inadequate dietary calcium intake can be supported through calcium supplementation, as adequate calcium intake is important to reduce bone loss, and trials of osteoporosis treatments have included adequate calcium intake.

Controversy around the use of calcium supplementation (but not dietary calcium intake) persists because of concerns regarding increased vascular events in some but not all studies.[12-15] Although there is no good direct evidence that calcium supplementation reduces fracture rates, calcium supplementation has been shown to increase BMD, especially in those with low baseline BMD, low dietary calcium intake or low vitamin D levels (<25 nmol/L), as well as in older people and in women taking menopausal hormone therapy.[16] In the Women's Health Initiative (WHI) study, calcium supplementation was also associated with an increased risk of kidney stones, although this group had an average baseline calcium intake of 1150 mg/day (higher than the average Australian intake of 741 to 781 mg/day).[17,18] Thus, calcium supplementation at a daily dose of 500 to 600 mg may be warranted in people with insufficient dietary intake after discussion of the potential risks.[19]

Calcium supplements are available as calcium carbonate or calcium citrate and typically contain 250 to 600 mg of elemental calcium per tablet. Calcium citrate may be preferred in people taking proton pump inhibitors, as it can be absorbed in the absence of an acidic environment.

Vitamin D

Vitamin D increases calcium absorption and is important for bone mineralisation. Vitamin D is generated in the skin after exposure to ultraviolet light and is then converted to the active form through two hydroxylation steps. The first step, in the liver, produces inactive 25-hydroxyvitamin D, the form measured in serum for diagnosis. The second step, in the kidneys, produces 1,25-dihydroxyvitamin D (calcitriol), the active form. The recommended sun exposure to achieve adequate vitamin D levels is five to 15 minutes of sunlight (depending on the time of year and latitude) four to six times a week, and longer for those with darker skin. Those at risk for vitamin D deficiency include office workers, people in residential aged care and other institutions, and people who wear skin coverings for personal, cultural or religious reasons. Although the optimal targets for bone and muscle health are debatable, serum 25-hydroxyvitamin D levels of 50 nmol/L and above at the end of winter (consider allowing 10 to 20 nmol/L higher at the end of summer to allow for seasonal change) are currently considered adequate. Levels from 12.5 to 49 nmol/L are considered insufficient, and less than 12.5 nmol/L is severely deficient.[20] Oral supplementation with 1000 to 2000 IU of colecalciferol (vitamin D_3) daily (maintenance dose) is usually adequate to treat insufficiency. Doses of 3000 to 5000 IU daily for three months, followed by a maintenance dose, are usually adequate for severe deficiency. If a patient has insufficient serum 25-hydroxyvitamin D levels despite usual oral replacement doses, malabsorption should be suspected.

A meta-analysis found that 800 IU of vitamin D daily reduced hip fractures by 30% and nonvertebral fractures by 14% in people over 65 years of age, regardless of age group, type of dwelling, baseline 25-hydroxyvitamin D level and additional calcium intake.[21] A review of small trials suggested that daily vitamin D supplementation may reduce mortality among institutionalised elderly people and reduce risk of falls but not fractures.[22]

The use of high-dose vitamin D supplementation has been explored as a means of circumventing noncompliance, with one study finding an increase in falls and fractures after a single annual

TABLE. DRUGS AVAILABLE IN AUSTRALIA FOR THE MANAGEMENT OF OSTEOPOROSIS* *continued on next page*

Drug name	Dosage	Fracture reduction	Current PBS indication	Side effects	Clinical practice points
Bisphosphonates					
Alendronate	70 mg weekly oral	VF: 50% HF: 51–56% NVF: 20–35%	• Treatment for OP† • Previous fracture† • Corticosteroid-induced OP§ *(Streamlined authority for combination with calcium or vitamin D required for all three indications)*	• Oesophagitis (reduced with enteric-coated tablets) • Musculoskeletal symptoms • Rare: ONJ, AFF	• Check before treating that patient's serum 25-hydroxyvitamin D level is adequate • Caution in renal impairment • To improve absorption, tablets should be taken on an empty stomach, sitting upright, 30 minutes before any other food or drink (unless using the enteric-coated risedronate tablets)
Risedronate	35 mg weekly oral or 150 mg monthly oral	VF: 41–49% HF: 30% NVF: 33–40%	• Treatment for OP† • Previous fracture† • Corticosteroid-induced OP§ *(Streamlined authority for combination with calcium or vitamin D required for the above three indications)* • Preservation of BMD‖ *(Authority required)*		
Zoledronic acid	5 mg yearly intravenous	VF: 70% HF: 41% NVF: 25%	• Treatment for OP† • Previous fracture† • Corticosteroid-induced OP§ *(Streamlined authority required for all three indications)*	• Acute-phase response • Musculoskeletal symptoms • Hypocalcaemia • Rare: ONJ, AFF	• Check before treating that patient's serum 25-hydroxyvitamin D level is adequate • Caution in renal impairment • Dosing interval may be increased • Infusions can be arranged through local infusion centres or hospitals
Oestrogens and oestrogen-related therapy					
Raloxifene	60 mg daily oral	VF: 30–35% NVF: NS	• Previous fracture‡ *(Streamlined authority required)*	• Venous thromboembolism • Exacerbation of menopausal symptoms • Leg cramps • Nausea	• Reduction in risk of breast cancer
Menopausal hormone therapy					
Combined oestrogen and progesterone	–	VF: 35%¶ HF: 33%¶ Peripheral: 29%¶ Total: 24%¶	• Not PBS-listed for fracture prevention	• Venous thromboembolism • Increased risk of breast cancer • Cardiovascular disease and stroke	• Consider in perimenopause or early menopause • Progesterone to be added if the woman has an intact uterus
Oestrogen alone	–	VF: 38%** HF: 39%** Total: 30%**			
Tibolone	1.25 mg daily oral	VF: 45% NVF: 26%	• Not PBS-listed for fracture prevention	• Increased stroke in patients > 60 years of age	• Reduction in risk of breast and colon cancer • Benefits other menopausal symptoms

TABLE. DRUGS AVAILABLE IN AUSTRALIA FOR THE MANAGEMENT OF OSTEOPOROSIS* *continued from previous page*

Drug name	Dosage	Fracture reduction	Current PBS indication	Side effects	Clinical practice points
Biologic					
Denosumab	60 mg six-monthly subcutaneous	VF: 68% HF: 40% NVF: 20%	• Treatment for OP† • Previous fracture‡ *(Streamlined authority required for both indications)*	• Cellulitis or skin reaction • Hypocalcaemia • Rare: ONJ, AFF	• Check before treating that patient's serum 25-hydroxyvitamin D level is adequate • Strict six-monthly dosing
Anabolic					
Teriparatide	20 µg daily subcutaneous	VF: 65% HF: NS NVF: 35%	• Treatment for severe OP†† *(Authority required)*	• Nausea • Leg cramps • Skin reactions • Rare: hypercalcaemia, osteosarcoma	• Total lifetime exposure limited to 18 months in Australia • Consolidation with antiresorptive agent at conclusion of treatment

Abbreviations: AFF = atypical femoral fracture; HF = hip fracture; NS = not significant; NVF = nonvertebral fracture; ONJ = osteonecrosis of the jaw; OP = osteoporosis; VF = vertebral fracture.
* All treatments are approved for single-agent use only in Australia.
† BMD T-score ≤-2.5 and over 70 years of age. For zoledronic acid, BMD criteria is BMD T-score ≤-3.0.
‡ Fracture documented on plain x-ray or computed tomography (CT) scan or magnetic resonance imaging (MRI) scan. A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
§ Patient must be on long-term (at least three months), high-dose (at least 7.5 mg daily prednisolone or equivalent) corticosteroid therapy and BMD T-score ≤-1.5.
‖ Patient must be on long-term (at least three months), high-dose (at least 7.5 mg daily prednisolone or equivalent) corticosteroid therapy and BMD T-score ≤-1.0.
¶ Fracture reduction from trials using conjugated equine oestrogen 0.625 mg daily and medroxyprogesterone acetate 2.5 mg daily.
** Fracture reduction from trials using conjugated equine oestrogen at 0.625 mg daily.
†† BMD T-score ≤-3.0 and patient has had two or more minimal trauma fractures and at least one symptomatic new fracture after 12 months continuous therapy with an antiresorptive agent at adequate doses. Specialist endocrinology or consultant physician input required.

oral dose of 500,000 IU of colecalciferol and another finding no benefit with an annual intramuscular injection of 300,000 IU of ergocalciferol (vitamin D_2) in community dwellers over 75 years of age.[23,24] Current recommendations support a daily dose of 600 to 1000 IU colecalciferol orally.[19] High-dose oral supplements are also available from compounding chemists for patients requiring ongoing high doses.

Pharmacological therapies

Pharmacological therapies can be classified as either antiresorptive (i.e. targeting osteoclast-mediated bone resorption) or anabolic (i.e. stimulating bone formation by osteoblasts). In Australia, there is one anabolic therapy agent available (teriparatide). All available agents improve BMD and reduce fractures and are currently approved for use as single agents. The Table and Figure summarise the fracture reduction efficacy, PBS indication, side effects, clinical practice points and mechanism of action of agents currently available in Australia.

Bisphosphonates

Bisphosphonates inhibit bone remodelling by inducing osteoclast apoptosis and osteoclast-mediated resorption. Alendronate, risedronate and zoledronic acid have all been shown to reduce vertebral fractures (by 40 to 70%), hip fractures (by up to 55%) and nonvertebral fractures (by 25 to 40%).[25-32] Zoledronic acid has also been shown to reduce mortality after hip fracture in excess of the mortality benefit expected from fracture reduction alone.[33,34] The exact mechanisms for the mortality reduction are unknown. Although zoledronic acid is approved for an annual infusion, the antiresorptive action may extend to 18 months, and less frequent administration may remain efficacious.[35,36]

Bisphosphonates are poorly absorbed enterally (<1%) and should not be prescribed in those with oesophageal disease. To maximise absorption, it is recommended that oral bisphosphonates be taken on an empty stomach with water after an overnight fast, at least 30 minutes before any food or drink, and in an upright position. However, enteric-coated delayed-release risedronate can be taken with food (as long as it is not calcium rich). Absorption may also be impaired if a bisphosphonate is taken concurrently with calcium, a proton pump inhibitor or a histamine-2 receptor antagonist.

Mild adverse effects of bisphosphonates include gastrointestinal symptoms, hypocalcaemia and myalgia with an influenza-like illness. The risk of hypocalcaemia can be minimised by ensuring 25-hydroxyvitamin D sufficiency before treatment is started. An influenza-like illness has been observed in up to 20% of patients treated with intravenous zoledronic acid, but is usually limited to after the first dose and can be managed with regular paracetamol for 72 hours. Bisphosphonates should be used with caution in patients with renal impairment (estimated creatinine clearance <30 mL/min/1.73 m^2).

More serious but very rare adverse effects of bisphosphonates include atypical

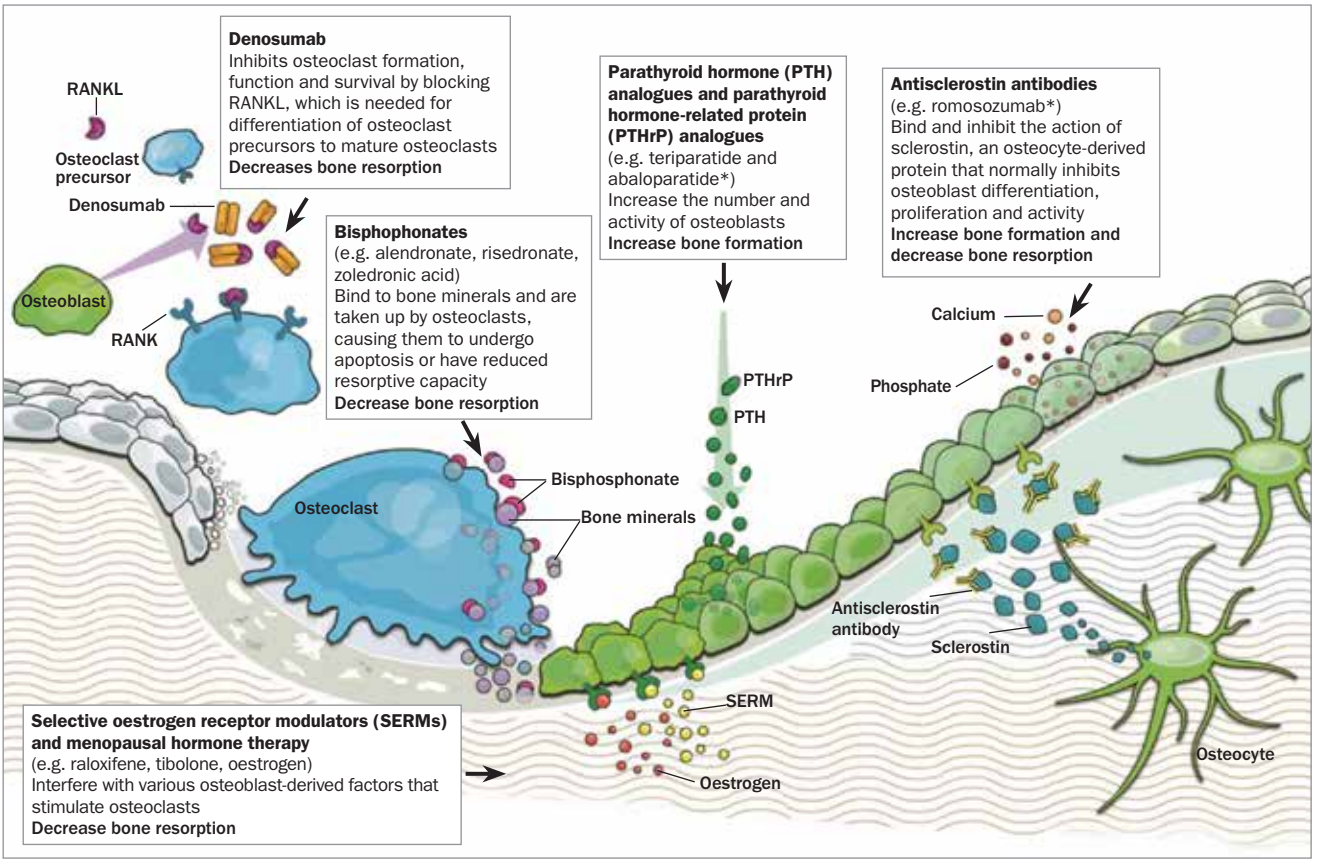

Figure. Mechanism of action of treatments for osteoporosis.

Abbreviations: RANK = receptor activator of nuclear factor kappa-B; RANKL = receptor activator of nuclear factor kappa-B ligand.

* Abaloparatide and romosozumab are not available in Australia.

Adapted with permission from: Connelly D. Osteoporosis: moving beyond bisphosphonates (infogaphic). The Pharmaceutical Journal 2016; 297: 23 Nov. doi: 10.1211/PJ.2016.20201978.

femoral fracture (AFF) and osteonecrosis of the jaw (ONJ). An AFF can be considered a stress fracture and is characteristically transversely orientated, in the subtrochanteric femur, with focal lateral cortical beaking and noncomminuted morphology. Clinically, there may be a prodromal dull ache in the femur, and up to 50% of cases are bilateral. If an AFF is suspected, bilateral femoral radiographs should be requested. The exact pathophysiological mechanism is unknown, although it has been postulated to relate to excessive suppression of bone turnover, as some studies have found an association between AFF and more than five years of bisphosphonate use.[37] However, biopsy data do not support this hypothesis.[38] The risk is also increased with corticosteroid use. The incidence is low, ranging from approximately two in 100,000 to five in 10,000 patients taking bisphosphonates; conservative calculations of benefit-to-risk ratio are therefore highly in favour of treatment for at least five years in postmenopausal women.[39]

ONJ is defined as exposed bone in the oral maxillofacial region that does not heal within eight weeks.[40] Similarly to AFF, the incidence is very low in patients with osteoporosis (one in 10,000 to 100,000 patient-years of bisphosphonate use), with higher rates reported in patients with cancer (treated with higher doses and higher frequency of intravenous bisphosphonates). Risk factors include dentoalveolar surgery, concomitant oral disease, use of glucocorticoids or immunosuppressants, diabetes and cigarette smoking. Strategies to minimise the risk of ONJ include stabilisation of oral disease before initiating antiresorptive treatment, maintaining good oral hygiene, and potentially withholding antiresorptive therapy until the surgical site heals with complete mucosal coverage. If required, dental assessment and treatment should be considered before bisphosphonate treatment is started, particularly in people at high-risk.

In light of concerns about risks associated with long-term treatment, a 'drug holiday' after five years has been suggested, although the exact timing and duration are unclear. In the extension trials of alendronate and zoledronic acid, beneficial effects on BMD and bone turnover markers were retained for up to five years, after five years and three years of use, respectively.[41,42] However, there was a reduction in vertebral (but not

nonvertebral) fractures in those who continued therapy compared with those who discontinued bisphosphonates. There was also ongoing reduction in nonvertebral fractures in those who continued therapy even in those with BMD in the nonosteoporotic range. It should be noted, however, that these trials were not powered to assess fracture reduction. Current recommendations are to review ongoing treatment at five years, and if the patient has a low BMD (T-score ≤-2.5), previous vertebral fracture and/or any recent fracture continuation of treatment is usually warranted.

Raloxifene

Raloxifene, a selective oestrogen receptor modulator (SERM), acts like oestrogen at the skeleton to maintain BMD at the hip and spine and reduce vertebral fractures. It has been studied in both prevention as well as treatment of osteoporosis,[43,44] and vertebral fracture reduction was shown to be 30 to 35%; however, there is no evidence for reduction of hip or peripheral fractures.

The nonbone benefits of raloxifene therapy include an improved lipid profile and reduction in breast cancer risk, but it exacerbates menopausal symptoms including hot flushes and increases the risk of venous thromboembolism.

Menopausal hormone therapy

Menopausal hormone therapy (combined oestrogen and progesterone or oestrogen alone) has been shown to be efficacious in reducing the number of vertebral and nonvertebral fractures in postmenopausal women, with efficacy equivalent to that of bisphosphonates.[45,46] The potential cardiovascular and mortality effects have been debated in light of the results from the WHI study, and emerging evidence favours the use of menopausal hormone therapy for preventing and treating osteoporosis (off label) in women in the perimenopausal or early menopausal stages after careful consideration of clinical risk factors.

Tibolone

Tibolone is a synthetic steroid and works as a selective tissue modulator of oestrogenic activity at different tissues. Tibolone reduces the risk of vertebral and nonvertebral fractures with similar efficacy to bisphosphonates, while also reducing the risk of breast and colon cancers.[47] There is, however, evidence of increased risk of stroke among people taking tibolone who are over 60 years of age, but no definite increase in coronary heart disease or venous thromboembolism.

Other oestrogen-related benefits include fewer hot flushes and vaginal symptoms. The progestogenic benefits of tibolone include protection from endometrial thickening (thus co-treatment with progesterone in women with an intact uterus is not required), and the androgenic benefits include improvement in mood and libido. Tibolone may be an alternative for women with other menopausal symptoms in the early postmenopausal stage.

Denosumab

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor kappa-B ligand (RANKL) and inhibits osteoblast-initiated osteoclast activation and function. It is a potent antiresorptive agent that has been shown to reduce vertebral fractures by 68%, nonvertebral fractures by 20% and hip fractures by 40%.[48] Extension studies for a total of eight years of treatment have shown ongoing benefits in BMD gains and fracture reduction.[49]

Two important practical differences set denosumab apart from the bisphosphonates. First, denosumab may be used in patients with chronic kidney disease, although the risk of hypocalcaemia is higher due to abnormal underlying bone metabolism even with normal 25-hydroxyvitamin D levels, and monitoring of serum calcium levels should be considered after injection in those with chronic kidney disease stage IV and above. Second, the effect of one dose wears off after six months, with a subsequent rapid increase in bone turnover, placing patients at a high risk of rapid bone loss and potential fracture if a subsequent dose is missed. The maximum safe time delay between doses is unknown, as high bone turnover persists for up to one year after treatment cessation.[50] A gap in therapy of over one month is unadvised. As with the bisphosphonates, ONJ and AFF occur rarely in patients taking denosumab.

Strontium

Strontium ranelate increases BMD by its incorporation into bone and through reducing osteoclast-induced resorption. It has been shown to reduce vertebral and nonvertebral fractures;[51,52] however, recent concerns regarding cardiovascular events and venous thrombosis led to the addition of a black-box warning to product information to highlight the restricted indication.[53] Based on reanalysis of its cost-effectiveness, strontium ranelate is no longer PBS listed.[54]

Teriparatide

Teriparatide is a recombinant form of human parathyroid hormone and is the only anabolic therapy currently available in Australia. It has been shown to reduce the risk of vertebral fractures by 65% and nonvertebral fractures by 35%, but no difference was seen with hip fractures.[55] It is currently approved in Australia for severe osteoporosis with a maximum of 18 months' treatment. Consolidation therapy with an antiresorptive drug after the 18-month treatment course is recommended to maintain BMD gains.

Contraindications include primary hyperparathyroidism, hypercalcaemia, Paget's disease and previous radiotherapy to bone. It should not be given in active malignancy. In rat studies, osteosarcoma was increased when rats were given lifetime superhuman doses of teriparatide, and although postmarketing surveillance has not detected an excess of teriparatide-related osteosarcoma in humans, it is for this reason that therapy is restricted in Australia to 18 months. The positive effects of parathyroid hormone on bone formation may be attenuated by previous long-term use of bisphosphonates.

Emerging therapies

Abaloparatide, an analogue of parathyroid hormone-related peptide, has been shown to reduce new vertebral and nonvertebral fractures in postmenopausal women.[56] It is currently only available in the USA (approval in Europe is under review).

Romosozumab, an antisclerostin antibody, is a promising anabolic agent. Sclerostin is a glycoprotein produced by osteocytes that inhibits osteoblast differentiation. Romosozumab has been shown to increase bone formation and BMD, and in a recent randomised placebo-controlled trial it significantly reduced vertebral fractures by 73% and all fractures by 36%.[57] A large international trial is under way comparing romosozumab with bisphosphonates.

Odanacatib, an inhibitor of cathepsin K (an osteoclast-produced enzyme involved in bone resorption), was shown in a very large international randomised placebo-controlled trial to be associated with significant reduction in vertebral, hip and peripheral fractures. However, because of an increase in stroke, all further drug development has ceased.

Conclusion

Osteoporosis is a common condition with significant morbidity and mortality from increased fractures. Nonpharmacological methods have a small role in prevention and also have an adjunctive role in treatment of established osteoporosis. There are multiple effective pharmacological treatments with various side effect profiles, and therapy should be individualised after consideration of the risks and benefits. Preventing future fractures is paramount to maintaining an individual's independence with osteoporosis and minimal trauma fractures the benefits of pharmacological therapy far outweigh the small risk of side effects. Thus all patients with osteoporosis and minimal trauma fractures should be assessed and considered for active therapy. Although osteoporosis in postmenopausal women is common, secondary causes should always be considered and excluded in patients with severe disease before commencing antiosteoporotic therapy. MT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

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