ARTICLE

Treating osteoporosis: risks and management

Jimmy Zhu
Physician trainee, Royal North Shore Hospital, Sydney

Lyn March
Consultant rheumatologist and Head, Department of Rheumatology, Royal North Shore Hospital, Sydney

Liggins Professor, Rheumatology and Musculoskeletal Epidemiology, Northern Clinical School, University of Sydney

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SUMMARY

Osteoporosis, osteopenia and minimal trauma fractures are becoming increasingly common in the ageing population. Fractures cause increases in morbidity and mortality and have a significant financial impact on the healthcare system and society.

Addressing risk factors for osteoporosis early may prevent or delay the onset of fractures and use of drugs. Calcium and vitamin D supplementation may benefit people with a high risk of deficiency (e.g. institutionalised older people) but may not be required in people without risk factors. Impact and resistance exercises and physical activity can increase bone density and prevent falls.

Antiresorptive drugs such as bisphosphonates and denosumab remain first-line treatment options for osteoporosis. The ongoing need for bisphosphonates should be assessed after five years and treatment may then be interrupted in some patients. Progressive bone loss will recur slowly. Denosumab therapy should not be interrupted without switching to another therapy, as post-treatment bone loss can progress rapidly. All patients will need ongoing monitoring and most will require some long-term therapy once started.

Raloxifene may be considered in women who do not tolerate first-line antiresorptive drugs. Romosozumab is a new anabolic treatment for osteoporosis and, together with teriparatide, is subsidised as second-line therapy for individuals with severe disease and multiple fractures. Specialist referral should be considered for patients who sustain fractures while undergoing osteoporosis therapy.

Introduction

Osteoporosis is a common musculoskeletal disease in older people characterised by a progressive loss in bone mineral density and microarchitectural deterioration. In Australians aged over 50 years, 40–60% of women and 25–30% of men will experience a minimal trauma fracture in their lifetime.[1] Fractures cause pain, disability and a reduced quality of life,[2] and are associated with an increased re-fracture rate. Fractures lead to a five-year mortality rate of 25%, which increases to up to 50% in the event of a re-fracture.[3] The population-attributable mortality risk associated with fractures in Australians aged 45 years and over has been found to be similar to that associated with cardiovascular diseases and diabetes, highlighting the need to identify and treat osteoporosis.[4]

Osteoporosis is a silent disease before a fracture occurs, so the exact prevalence is hard to determine. Even after diagnosis, it is often undertreated, with approximately 25% of Australian patients with osteoporosis having no history of receiving osteoporosis medicines.[5]

Osteoporosis risk assessment

There are a number of non-modifiable and modifiable risk factors, diseases and drugs associated with osteoporosis and minimal trauma fractures. The fracture risk for an individual can be accurately predicted using the Garvan Fracture Risk or FRAX calculators.[6,7] Age, a family history of hip fractures and previous fractures are key risk factors. All men and women over the age of 50 years who have sustained a fracture have a higher risk of subsequent fractures and should be assessed and considered for treatment. Bone mineral density testing is also recommended and subsidised for all men and women over 70 years of age. Along with falls-risk screening, it is recommended as part of general health checks for all individuals, yet medical record audits indicate that this prevention strategy is currently underused.[8]

Osteoporosis can be defined using bone mineral density testing, which generates a T-score and Z-score. The T-score reflects the number of deviations from the peak bone mass of age-, sex- and ethnicity-matched norms. A T-score less than –2.5 indicates a significant reduction in bone mass. The Z-score reflects the number of standard deviations from the average bone mass of age-, sex- and ethnicity-matched norms. A Z-score less than –2.0 should prompt a more complete search for secondary causes of osteoporosis.

Management strategies

Addressing lifestyle risk factors, appropriately treating predisposing conditions and minimising the unnecessary prescription of drugs associated with osteoporosis may slow the decline in bone

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density and prevent minimal trauma fractures. Some modifiable risk factors are summarised in the Box.[9] Various management strategies can help decrease the risk of osteoporosis or delay its onset.

Exercise

Exercise throughout a person's lifetime can delay the onset of osteoporosis. Exercise in children and adolescents is strongly associated with a higher peak bone density in adulthood. This effect is seen most with high-impact exercises such as hopping, skipping and jumping.[10] Even an increase in leisurely physical activity can cause a durable increase in bone mass that can persist into early old age.[11] In older people, low-impact exercises such as walking and swimming may slow the decline in bone mass, whereas higher impact exercises, resistance exercises, and combinations of different types of exercises may increase bone density.[12-15]

The frequency and severity of falls may also be reduced by exercise programs, such as Stay On Your Feet and Stepping On. The main benefits are seen with programs focused on balance and function, or programs that involve multiple types of exercise (e.g. balance exercise plus resistance exercise).[16] Where possible, individuals are encouraged to perform a combination of weight-bearing, resistance and balance exercises. Information regarding the types of exercises that can be recommended is available from the Healthy Bones Australia fact sheets.

Calcium

Adequate calcium concentrations are crucial to prevent bone loss and fractures. The recommended dietary intake of calcium is 1000–1300 mg per day, depending on age and sex. Common calcium-rich foods include dairy products, chickpeas, beans, sardines and tofu. A dietary calcium calculator is available on the International Osteoporosis Foundation website.

Most older Australians do not achieve the recommended dietary intake of calcium. Along with information and guidance on dietary modifications, daily supplements of 500–600 mg are sometimes needed for these people. Calcium supplementation, particularly with vitamin D, can reduce the rate of bone loss and fractures in people who are deficient in calcium such as frail elderly people.[17]

There is conflicting evidence regarding oral calcium supplementation and the risk of major adverse cardiac events, which include myocardial infarction and stroke. Recent meta-analyses on cardiovascular disease risk have revealed a range from a 10% relative risk reduction to a 15% relative risk increase.[18-20]

Vitamin D

Vitamin D is important for the absorption and use of calcium in the body. Evidence suggests about a third of Australians have vitamin D deficiency.[21] While small amounts of vitamin D are absorbed through food, most is received from direct sunlight. Those with fair skin require 6–7 minutes of mid-morning or mid-afternoon sun exposure outdoors during the summer and up to 30 minutes during the winter to maintain adequate concentrations of vitamin D. People with darker skin will require 3–6 times the length of exposure. Additionally, window glass, full-coverage clothing and sunscreen inhibit the transmission of ultraviolet B radiation and thus vitamin D synthesis in the skin. Vitamin D synthesis is also less efficient in older people.[22] Improving vitamin D concentrations reduces the risks of falls and fractures in older people,[23,24] particularly when combined with adequate calcium concentrations.[17,25]

Box **Factors associated with osteoporosis and minimal trauma fractures**[9]

Lifestyle	Conditions	Drugs
Increased falls risk	Endocrine diseases	Glucocorticoids
• poor balance	Sex hormone deficiency	Excessive thyroid hormone replacement
• vision impairment	Cushing syndrome	Androgen deprivation therapy
Sarcopaenia	Hyperthyroidism	Aromatase inhibitors
Smoking	Hyperparathyroidism	Proton pump inhibitors
Alcohol consumption	Diabetes mellitus	Thiazolidinediones
Physical inactivity	Impaired gastric absorption	Selective serotonin reuptake inhibitors
Low calcium intake	Coeliac disease	Long-term heparin
Vitamin D deficiency	Upper gastrointestinal surgery	Antiepileptics
Low protein intake	Rheumatoid arthritis	Cyclophosphamide
		Sedating drugs
		Antihypertensives

Routine vitamin D supplementation for primary prophylaxis is not recommended for community-dwelling adults.[26] Those who have risk factors or symptoms of vitamin D deficiency should have their vitamin D concentrations measured. These are ideally measured in late winter or early spring, when serum 25-hydroxyvitamin D concentrations are the lowest. Optimal mineral metabolism, bone density and muscle function are achieved when serum 25-hydroxyvitamin D concentrations are greater than 50 nanomol/L. If testing is carried out in late summer, the concentration should be 10–20 nanomol/L higher.

Patients with vitamin D deficiency should start supplementation (Table 1). Routine vitamin D and calcium supplementation reduces the risks of falls and fractures in people with established osteoporosis or institutionalised people.[17] There are very few adverse effects related to oral vitamin D supplementation. When combined with calcium, there is a small risk of hypercalcaemia, nephrolithiasis and gastrointestinal symptoms.

Drugs for osteoporosis

Pharmacotherapy is indicated for individuals with a significantly increased risk of fractures. First-line treatment is available under the Pharmaceutical Benefits Scheme (PBS) for:

- those 50 years of age and over who have sustained a minimal trauma fracture
- those 70 years of age and over with established osteoporosis
- those who require long-term corticosteroids (minimum three months) on at least 7.5 mg of prednisolone or equivalent per day.

Antiresorptive therapy can reduce the risk of fractures by up to 50%. There is a consensus to treat individuals who have a hip fracture risk of more than 3% or any fracture risk of more than 20% over 10 years.[9] However, treatment for this indication alone is not subsidised under the PBS. There should be a shared discussion taking a patient's fracture risk, preferences and costs into consideration, although many drugs such as bisphosphonates are inexpensive.

Before starting drugs for osteoporosis, ensure that all patients have adequate vitamin D and calcium concentrations and that any secondary causes for osteoporosis have been managed. Table 2 summarises the common and notable rare adverse effects of different osteoporosis treatments.

Bisphosphonates

Bisphosphonates inhibit osteoclast activation and prevent bone resorption. They slow the rate of bone loss, improve bone mineral density and reduce both hip and vertebral fractures. Alendronate, risedronate and zoledronic acid are currently available for osteoporosis in Australia. Head-to-head evidence for bisphosphonates is lacking. At the time of publication, bisphosphonates are cheaper than other drug treatments.

Oral and intravenous bisphosphonates are contraindicated in patients with renal impairment and should be avoided if the estimated glomerular filtration rate is less than 35 mL/minute/1.73 m^2.[27]

Safety data are robust for the use of oral bisphosphonates up to five years and intravenous bisphosphonates up to three years.[28] The fracture risk should then be re-assessed, and most specialists normally extend treatment if the patients fall under any of the following high-risk categories:

- femoral neck T-score less than –2.5
- femoral neck T-score less than –2.0 with vertebral fractures
- a recent fracture.

Oral and intravenous bisphosphonates can be extended up to 10 and six years, respectively, without an increase in adverse events compared to placebo.[28-34] Treatment extension in these high-risk populations has been shown to be effective in preventing new vertebral fractures, but minimally beneficial for preventing hip fractures. Patients at lower risk have not been shown to experience more clinical fractures

Table 1 **Initial treatment of vitamin D deficiency**

Vitamin D status	25-hydroxyvitamin D concentration (at the end of winter)	Recommended vitamin D supplementation*	Follow-up
Mild deficiency	30–49 nanomol/L	1000–2000 IU per day	3–5 months after starting supplementation; annually recommended if receiving treatment for osteoporosis
Moderate deficiency	12.5–29 nanomol/L	3000–5000 IU per day (for 6–12 weeks) followed by a maintenance dose of 1000–2000 IU per day	
Severe deficiency	<12.5 nanomol/L		

* Alternatively, higher doses may be given less frequently when needed.

Table 2 **Adverse effects of osteoporosis drugs**

Drug	Common adverse events	Notable rare adverse events
Oral bisphosphonates	Hypocalcaemia Upper gastrointestinal effects (gastro-oesophageal reflux, erosive oesophagitis)	Osteonecrosis of the jaw* Atypical femoral fractures†
Intravenous bisphosphonates	Hypocalcaemia Flu-like illness following infusion	Osteonecrosis of the jaw* Atypical femoral fractures†
Denosumab	Hypocalcaemia Injection-site reactions Atraumatic vertebral fractures following discontinuation	Osteonecrosis of the jaw* Atypical femoral fractures†
Raloxifene	Hot flushes Venous thromboembolism	Stroke
Teriparatide	Hypercalcaemia Injection-site reactions	Theoretical risk of osteosarcoma
Romosozumab	Injection-site reactions	Possible increased risk of major adverse cardiovascular events (myocardial infarction, stroke) Osteonecrosis of the jaw* (few case reports) Atypical femoral fractures† (few case reports)

* Risk factors include dental extractions, implants, poorly fitting dentures, pre-existing dental disease, glucocorticoid use and smoking.
† Risk factors include rheumatoid arthritis, increased femoral bowing, thicker lateral cortices at the femoral shaft and Asian ethnicity.

after stopping therapy due to the durable effects of bisphosphonates.[28-34] If therapy is stopped, the fracture risk is generally re-assessed in 2–3 years or upon re-fracture to consider restarting therapy.

Oral bisphosphonates

Alendronate and risedronate are inexpensive and have once-weekly or once-monthly oral dosing. It is important to counsel patients to take oral bisphosphonates in the morning on an empty stomach with a full glass of water and to remain upright for 30 minutes after ingestion to ensure adequate drug absorption and prevent erosive oesophagitis. The main limitations of oral bisphosphonates are their upper gastrointestinal effects. Dysphagia, achalasia or an inability to remain upright for 30 minutes after tablet ingestion are absolute contraindications. They should also be used with caution in patients who have previously undergone upper gastrointestinal or bariatric surgery, as this may impair drug absorption and increase the risk of adverse events.

Intravenous bisphosphonates

Zoledronic acid is an intravenous bisphosphonate given as an annual infusion. It can help overcome the gastrointestinal limitations of oral formulations, but it has other potential adverse effects, most notably the risk of flu-like reactions following infusions. Myalgias and arthralgias can also occur and may be prolonged. Patients with renal impairment can be at greater risk of these reactions, and in such cases, the infusion rate could be reduced. Alternatively, a different class of drug that is not affected by renal function, such as denosumab, should be considered. There is also a small risk of atrial fibrillation and uveitis with intravenous zoledronate. Bisphosphonates have been associated with the rare and serious adverse events of atypical femoral fractures and osteonecrosis of the jaw.

Denosumab

Denosumab is a monoclonal antibody that reversibly inhibits bone resorption by reducing osteoclast formation and differentiation while increasing osteoclast apoptosis. It increases bone mineral density at the lumbar spine and hip and reduces the risk of fractures. Denosumab is administered as a six-monthly subcutaneous injection. In contrast to bisphosphonates, denosumab can be used in patients with chronic kidney disease. However, these patients are particularly at risk of hypocalcaemia, so baseline concentrations of calcium and vitamin D should be assessed before starting therapy.

Patients should either continue denosumab indefinitely or be transitioned to an alternative treatment drug (e.g. bisphosphonates) for at least 12 months on discontinuation. Unlike bisphosphonates, the effect of denosumab is not durable and is rapidly reversible

after cessation.[35] Stopping denosumab or missing doses is associated with an increased risk of atraumatic vertebral fractures.[35-39] The incidence of these fractures has been reported to be between 7% and 10%, with more patients sustaining multiple vertebral fractures compared to patients who have not received denosumab.[35-38] These rebound effects can be seen as early as seven months after the previous dose and can persist for two years following discontinuation.[38,39]

Bisphosphonates such as alendronate and zoledronic acid appear to be effective in minimising the bone loss and mitigating the increased fracture rate associated with denosumab discontinuation.[35,38,39] Between 2012 and 2017, over 80% of Australian patients receiving denosumab did not receive subsequent bisphosphonate treatment following cessation.[5] This number should decrease with increased awareness of the adverse effects of stopping denosumab. Denosumab has also been associated with the rare and serious adverse events of atypical femoral fractures and osteonecrosis of the jaw.

Raloxifene

Raloxifene is a selective oestrogen receptor modulator that reduces postmenopausal bone loss. It reduces the risk of vertebral fractures, but it does not reduce the risk of non-vertebral fractures. It is taken as a daily tablet, which patients may find inconvenient. Raloxifene is an alternative to bisphosphonates or denosumab (if they cannot be tolerated) for women with postmenopausal osteoporosis and may be appropriate for younger women with spinal osteoporosis soon after menopause. It increases the incidence of hot flushes, which can be a significant problem in young postmenopausal women. Raloxifene reduces the risk of breast cancer, so it can be considered in women with a high risk of breast cancer. However, it increases the risk of deep venous thrombosis, and other evidence suggests slightly increased mortality after stroke.[40]

Menopausal hormone therapy

Menopausal hormone therapy can consist of combined oral or transdermal oestrogen with oral progesterone therapy, or tibolone alone as a daily tablet. It is an effective option for women who require treatment for osteoporosis and have either premature menopause or significant postmenopausal symptoms requiring pharmacotherapy. Menopausal hormone therapy reduces the risk of all fractures, while tibolone has not been shown to reduce the risk of hip fractures.[41] While menopausal hormone therapy may be useful when osteoporosis and fracture prevention therapy is required in women younger than 50 years of age, the risks of this therapy must be considered with long-term use.[41,42]

Teriparatide

Teriparatide is a synthetic form of parathyroid hormone that stimulates bone formation. It is given as a once-daily subcutaneous injection. Teriparatide is used to treat severe osteoporosis and is subsidised for an 18-month treatment course in Australia when patients continue to sustain fractures and remain severely osteoporotic (T-score less than –2.5) despite receiving at least 12 months of first-line treatment. The rate of vertebral fractures may be reduced by up to 65%. Teriparatide has been shown to reduce non-vertebral and hip fractures by up to 55%.[43,44]

Contraindications include age younger than 25 years, known or suspected Paget's disease, previous radiotherapy to the bone and pre-existing hypercalcaemia, malignancy, kidney disease and primary hyperparathyroidism. Following the treatment course, patients should receive antiresorptive therapy (e.g. a bisphosphonate, denosumab, raloxifene) to maintain the improvements in bone density and the fracture risk reduction effect. Without this, the anabolic effects of these drugs are lost.

Romosozumab

Romosozumab is an antisclerostin monoclonal antibody that decreases bone resorption and increases bone formation. Similar to teriparatide, it is only subsidised in patients with severe osteoporosis who continue to sustain fractures despite receiving at least 12 months of first-line treatment. It is administered as two subcutaneous injections once a month for 12 months.

Romosozumab is superior to both alendronate and teriparatide in improving bone density at the spine and hip. It has been shown to reduce the relative risk of vertebral fractures by 73% compared to placebo, and by 48% compared to weekly alendronate. It has also been shown to reduce the risk of non-vertebral fractures by 19% and hip fractures by 38%.[45,46]

The ARCH trial demonstrated a small increase in the incidence of cardiovascular events in the romosozumab arm, which was not seen in other trials.[47] More supporting data are required, but romosozumab is currently not recommended for patients with a high risk of myocardial infarction or stroke. Other common adverse effects include injection-site reactions. Romosozumab should not be used for more than 12 months given the lack of long-term safety data. Following the treatment course, patients should receive antiresorptive therapy (e.g. a bisphosphonate, denosumab, raloxifene) to maintain the improvements in bone density and the fracture risk reduction effect. Without this, the anabolic effects of these drugs are lost.

Sequential treatment with first-line anabolics

There is evidence to suggest that the treatment sequence may be important in managing osteoporosis. The response to anabolic drugs such as romosozumab may be blunted by previous treatment with antiresorptive drugs. Some studies have shown superior and durable gains in bone density when anabolic drugs are given before antiresorptive drugs. More research is required to determine if the gains in bone density also correlate with a reduced fracture risk in these patients.[47] Given this evidence, for some treatment-naïve patients who present with severe osteoporosis (T-score less than –3.0) following a fracture, the option of first-line treatment with an anabolic drug such as romosozumab should be discussed with the patient. However, this is not a PBS-listed indication.

Monitoring osteoporosis

Repeat bone mineral density testing with dual-energy X-ray absorptiometry is useful to monitor a patient's response to therapy. It is recommended to test patients one year after starting or changing therapy, which can be spaced out to every 2–3 years if the bone density remains stable.[48] Annual testing is recommended in patients with accelerated bone loss, such as in patients using glucocorticoids.[48] It is important that serial bone density measurements are obtained using the same machine where possible as there can be significant variability between different models and clinics.

Bone turnover markers

Bone turnover markers may be useful in monitoring osteoporosis in some patients. The main bone turnover markers used in Australia are procollagen type 1 N-terminal propetide, which is a marker of bone formation, and C-terminal collagen telopeptide (CTX), which is a marker of bone resorption. Measuring the concentrations of these markers may be useful if there are concerns regarding reduced oral absorption due to previous surgery, a poor drug administration technique (e.g. taking oral bisphosphonates too close to mealtimes) or poor medication adherence.[49] As such, CTX testing is available once annually under the Medicare Benefits Schedule.

Conclusion

With our ageing population, the individual and economic impacts of osteoporosis will continue to rise. A combination of lifestyle and pharmacological strategies should be used to prevent fractures in older people, with effective screening tests available to identify those at higher risk. All men and women over the age of 50 years who sustain a fracture, and all those over 70 years of age regardless of whether they have sustained a fracture, should be assessed for antiresorptive therapy. Tailored impact and resistance exercises are safe and effective for preventing falls and can improve bone density.

Therapy can and should be tailored to each patient's preference for the mode of delivery and adverse-effect profile. Weekly (alendronate, risedronate) or monthly (risedronate) oral treatments and annual intravenous (zoledronate) or six-monthly subcutaneous injections (denosumab) are the preferred first-line treatments because of their ability to reduce the risk of vertebral and hip fractures. Other treatments are available for patients who cannot use or fail to respond to first-line treatment and continue to sustain fractures (raloxifene, teriparatide, romosozumab). Surveillance for potential adverse effects and the need to continue therapy is essential. <

Conflicts of interest: none declared

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