When to suspect and when to treat osteoporosis in men

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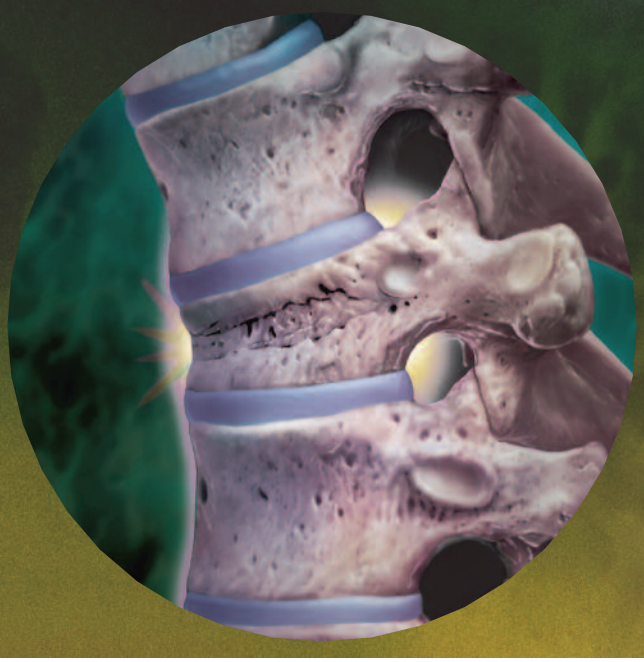
Osteoporosis is a significant cause of morbidity and mortality in men. There is now increasing evidence to support the use of various osteoporosis therapies in men and treatment should be considered in those with a high fracture risk.

Key points

- Osteoporosis in men is underdiagnosed and undertreated.
- Evaluation of men with a low bone mineral density and/or fragility fractures should include consideration of contributing secondary causes of osteoporosis.
- In addition to optimising calcium and vitamin D intake, all men with osteoporosis should be encouraged to undertake lifestyle modifications.
- Clinical studies are increasingly supporting the efficacy of most osteoporosis therapies in men.



Osteoporosis is an underdiagnosed and undertreated cause of morbidity and mortality in men. Although less common than in women, it confers a considerable health burden with one-third of all hip fractures worldwide occurring in men. One in six men will sustain a fracture by the age of 90 years, with almost half of these occurring before the age of 80 years.[1] Furthermore, hip fractures in men are associated with greater mortality, with reported mortality rates of up to 37.5% within a year of fracture.

Although data regarding the efficacy of antifracture therapy are primarily from clinical studies in postmenopausal women, there are increasing data to support the role of osteoporosis therapies in men.

Aetiology

Bone mass and strength is determined by both the attainment of peak bone mass and subsequent age-related bone loss, with the latter accelerating after the age of 70 years. Both of these processes are dependent on the action of sex steroid hormones, including testosterone and oestrogen. Significantly, most nonvertebral fractures occur in men without osteoporosis, implying that other factors distinct from bone mineral density (BMD) contribute to fracture risk.

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Hypogonadism occurs in almost one in eight men and is a significant contributor to osteoporosis in men due to the important role of sex steroid hormones in reducing bone resorption and loss. Men with hypogonadotropic hypogonadism and those taking androgen deprivation therapy for prostate cancer have a decreased BMD, increased bone turnover markers and higher fracture risk. This highlights the importance of assessing gonadal status and the potential therapeutic benefits of testosterone replacement.

Secondary causes of osteoporosis in men are common and need to be identified (see the box on page 9). Aside from hypogonadism, the most common secondary causes include glucocorticoid use, excessive alcohol intake and tobacco use.

Diagnosis and evaluation

Osteoporosis may be diagnosed after the occurrence of fragility fractures, although in most men it is asymptomatic. In the absence of minimal trauma fractures, the diagnosis of osteoporosis is based on BMD measurement, a robust predictor of fractures. Each standard deviation decrease in hip BMD, measured by dual energy x-ray absorptiometry, is associated with an increase in the relative risk of hip fracture. The diagnostic thresholds of BMD for osteopenia and osteoporosis that have been defined in men are similar to those in postmenopausal women, but should be interpreted in the context of male-specific T-scores. Bone densitometry is indicated in men aged 70 years or over, or in men aged over 50 years with risk factors for osteoporosis. Femoral neck BMD measurements are preferred because there may be artefactual elevation of spinal BMD measurements in older men due to conditions such as osteoarthritis or aortic calcification.

Evaluation of men with low BMD and/or fragility fractures should also include screening for secondary causes of osteoporosis. History may reveal the use of medications, such as glucocorticoids or androgen deprivation therapy, which may contribute to low BMD. Furthermore, a careful history and examination may suggest the presence of hypogonadism.

Initial investigations should include measurement of serum 25-hydroxyvitamin D, calcium and testosterone levels, in addition to assessment of renal and hepatic function, and a full blood count. The choice of further laboratory investigations is dependent on the results of the initial investigations. Further investigations may include the measurement of parathyroid hormone to exclude hyperparathyroidism; serum and urine protein electrophoresis; thyroid function tests; and screening tests for Cushing's syndrome (if clinical manifestations are present), coeliac disease and mastocytosis.

Secondary causes of osteoporosis

Common

- Cushing's syndrome or exogenous corticosteroid use (>5 mg/day for >three months)
- Excessive alcohol intake (more than two standard drinks per day)
- Primary or secondary hypogonadism (including androgen deprivation therapy)
- Inadequate calcium intake (<600 mg/day)
- Vitamin D deficiency/insufficiency
- Tobacco use

Less common

- Low body mass index (BMI <20 kg/m^2)
- Lack of exercise or excessive exercise
- Use of antiepileptic drugs (phenytoin, phenobarbitone, primidone, carbamazepine)
- Thyrotoxicosis
- Primary hyperparathyroidism
- Type 1 or type 2 diabetes
- Chronic liver or kidney disease
- Malabsorption, including coeliac disease
- Hypercalciuria
- Rheumatoid arthritis or ankylosing spondylosis
- Inflammatory bowel disease

Rare

- Multiple myeloma
- HIV infection or its treatment (e.g. tenofovir)
- Mastocytosis
- Immunosuppressive therapy (e.g. cyclosporin, tacrolimus)
- Osteogenesis imperfecta

Table 1. Suggested treatment thresholds for men with osteoporosis

Fracture risk		Intervention
Low risk	<8% five-year risk for any fracture <3% five-year risk for hip fracture	Lifestyle intervention
Moderate risk	>8% five-year risk for any fracture >3% five-year risk for hip fracture	Consider pharmacological therapy in addition to lifestyle intervention, especially if patient meets PBS subsidy criteria
High risk	>15% five-year risk for any fracture	Pharmacological therapy in addition to lifestyle intervention

Adapted from Osteoporosis Australia (see: http://www.osteoporosis.org.au/fracture-risk-calculators/).

Management

Decisions regarding the management of osteoporosis in men should be based on absolute fracture risk. Although BMD measurement is a key determinant of fracture risk, clinical risk factors, including age, past and parental history of fragility fractures, and gonadal status, are also significant. Risk assessment tools, such as the FRAX WHO fracture risk assessment tool and the Garvan Institute's fracture risk calculator, can be used to estimate the risk of fracture in men and help stratify the extent of interventions. Notably, fracture risk is generally underestimated by these assessment tools in men with diabetes as diabetes is not included as an independent risk factor.

Osteoporosis Australia recommends consideration of pharmacological therapy in men with greater than an 8% five-year risk of any fracture, or 3% five-year risk of hip fracture (Table 1). In the absence of contraindications, pharmacological therapy is indicated in any man who has experienced a minimal trauma fracture.

Nonpharmacological therapy

All men with osteoporosis should be encouraged to maintain an active lifestyle because reduced physical activity has been associated with increased bone loss and fractures.[2] In particular, high-intensity progressive resistance training and weight-bearing impact exercises have been shown to increase BMD. Other lifestyle modifications include balance and strengthening exercises, which have been shown to reduce falls in older people, tobacco cessation and the avoidance of excessive alcohol intake. In contrast, endurance training may augment spinal bone loss through its negative effects on levels of sex steroids and body weight.

Calcium supplementation provides modest benefits in terms of BMD and bone turnover markers. Osteoporosis Australia currently recommends a dietary calcium intake of 1000 to 1300 mg/day. Calcium supplementation (doses of 500 to 600 mg/day) can be taken if patients are not able to achieve these levels through diet alone. Although calcium intake and the risk of cardiovascular events is the subject of ongoing research and debate, calcium supplementation at these recommended doses (500 to 600 mg/day) is considered both safe and beneficial for most men.

Achieving adequate vitamin D levels is important for optimal musculoskeletal health. Suggested target levels for serum 25-hydroxy-vitamin D are 50 nmol/L or more at the end of winter, and 10 to 20 nmol/L higher at the end of summer. This may be attained through a combination of sunlight exposure, dietary intake and vitamin D supplementation. In older men, vitamin D, in addition to calcium supplementation, has been shown to reduce fracture and falls risk in meta-analyses of randomised controlled trials.[3,4]

Pharmacological therapy

Despite most clinical studies of antifracture therapy involving postmenopausal women, the efficacy and tolerability of these therapies appear to be similar in men. Various osteoporosis therapies have been shown to have beneficial effects on BMD and bone turnover markers in men. There are no head-to-head data comparing the various therapies.

The choice of pharmacological agent should ultimately be based on patient factors such as cost, compliance and safety. Table 2 lists the therapies available for osteoporosis in men and their PBS indications.

Oral bisphosphonates

As in women, bisphosphonates are a first-line treatment for osteoporosis in men. Numerous studies have demonstrated the efficacy of oral bisphosphonates in men, with both alendronate and risedronate reducing vertebral fractures, improving BMD and reducing bone resorption markers.[5,6] The use of alendronate in men with primary osteoporosis and a high fracture risk is supported by cost-effectiveness analysis.[7]

Zoledronic acid

The intravenous bisphosphonate zoledronic acid is also a first-line treatment for osteoporosis in men. It has the advantage of minimising gastrointestinal adverse effects and the annual infusion aids adherence to therapy. Potential adverse effects include an acute phase reaction with fever and myalgia, most commonly occurring after the first infusion, worsening of renal impairment and, very rarely, osteonecrosis of the jaw. Before administration of zoledronic acid, renal function and serum calcium levels should be assessed, and serum vitamin D should be repleted if deficiency is identified.

Early studies in men and women following a hip fracture reported that annual intravenous infusions of zoledronic acid reduced clinical fractures by 35% and were associated with a 28% reduction in mortality.[8] In a comparative study with alendronate, men expressed a preference for the annual intravenous infusion. The study also demonstrated similar effects of both bisphosphonates in terms of BMD and bone turnover markers.[9] A recently published randomised, controlled trial further supports the antifracture efficacy of zoledronic acid in men, reporting fewer vertebral fractures (1.6% *vs* 4.9%, p = 0.002) and significant improvements in BMD at all sites.[10]

Table 2. PBS indications for osteoporosis therapies in men*

Therapy	PBS indication
Osteoporosis	
Alendronate	Aged 70 years or older BMD T-score of -2.5 or less
Risedronate Strontium ranelate Zoledronic acid	Aged 70 years or older BMD T-score of -3.0 or less
Established osteoporosis	
Alendronate Risedronate Strontium ranelate	Minimal trauma fracture
Severe established osteoporosis	
Teriparatide	Treatment by a specialist BMD T-score of -3.0 or less Two or more minimal trauma fractures At least one symptomatic new trauma after at least 12 months' continuous antiresorptive therapy Treatment must be the sole PBS-subsidised agent Treatment must not exceed a lifetime maximum duration of 18 months
Corticosteroid-induced osteoporosis	
Alendronate Zoledronic acid	Long-term (at least three months), high-dose (at least 7.5 mg/day prednisolone [or equivalent]) glucocorticoid therapy BMD T-score of -1.5 or less
Risedronate	Long-term (at least three months), high-dose (at least 7.5 mg/day prednisolone [or equivalent]) glucocorticoid therapy BMD T-score of -1.0 or less

* The PBS indications are correct as of 1 June 2013.

Strontium ranelate

Strontium ranelate is another first-line treatment for osteoporosis in men. Recently published data in men have shown similar efficacy and cost effectiveness of strontium ranelate in postmenopausal women and men.[11,12] Although its mechanism of action is not fully understood, strontium ranelate has been shown to increase both BMD and bone alkaline phosphatase, a marker of bone formation, in men. Strontium ranelate is available in sachets containing 2 g granules for oral suspension. The recommended dose is one sachet daily two hours after meals.

Strontium ranelate is currently approved for the treatment of osteoporosis in men, and the PBS subsidy has recently been extended to include men (see the full schedule). Strontium ranelate has been associated with an increased risk of venous thromboembolism; significant cutaneous reactions, including drug reaction (or rash) with eosinophilia and systemic symptoms syndrome; and cardiac events.[13]

Denosumab

Denosumab, a monoclonal antibody that specifically targets receptor activator for nuclear factor kappa-B ligand, is an antiresorptive agent that is administered as a six-monthly subcutaneous injection. Although denosumab has been shown to reduce both vertebral and hip fractures in postmenopausal women, there are currently no comparable antifracture data in men. One study has shown improvements in BMD in men with primary osteoporosis.[14] Denosumab has also been shown to improve BMD and reduce vertebral fractures in men receiving androgen deprivation therapy for nonmetastatic prostate cancer.[15] It is currently only approved by the TGA for use in men receiving androgen deprivation therapy, but is not currently subsidised by the PBS for this indication.

Teriparatide

Teriparatide, or recombinant human parathyroid hormone (1-34), is a second-line drug for the management of osteoporosis in men. It is listed on the PBS (authority required) for men with severe established osteoporosis (BMD T-score of -3 or less) who have had two fragility fractures, and have experienced at least one new fracture after at least 12 months' continuous therapy with an antiresorptive

agent. Treatment is limited to a lifetime maximum of 18 months because of the potential for an increased risk of osteogenic sarcoma in animal studies, which has not been demonstrated in humans. Initiation of antiresorptive therapy after cessation of teriparatide is recommended as further gains in BMD will result.[16]

Teriparatide is an anabolic agent that promotes bone formation. Randomised controlled trials have shown that daily subcutaneous teriparatide significantly improves BMD and reduces vertebral fractures in both eugonadal and hypogonadal men.[17] It also reduces back pain in meta-analyses of randomised controlled trials.[18]

Secondary causes

Identification of secondary causes of osteoporosis allows treatment and, in some circumstances, elimination of the contributing factor.

Glucocorticoid-induced osteoporosis

Glucocorticoid-induced osteoporosis should be treated aggressively because significant bone loss occurs within the first few months of glucocorticoid therapy. Use of bisphosphonates has been shown to effectively increase BMD in men with glucocorticoid-induced osteoporosis. Bisphosphonate therapy is subsidised on the PBS for men receiving long-term high-dose bisphosphonates (≥ 7.5 mg for three months or more) with a BMD T-score of -1.0 or less.

Hypogonadism

In hypogonadal men, testosterone replacement therapy has a comparable effect to bisphosphonate therapy. Although the benefits of testosterone therapy on BMD and bone turnover markers are greatest in hypogonadal adolescents, studies in older men have demonstrated increased BMD with testosterone therapy. Eugonadal status should therefore be restored with testosterone replacement in men with high fracture risk and no contraindications to testosterone therapy. In the most severe cases, additional antifracture therapy would also be indicated.

The effects of testosterone therapy in eugonadal men remain controversial. Various studies have presented inconsistent findings regarding the effect of testosterone on BMD. Furthermore, due to potential risks of testosterone therapy, particular adverse cardiovascular outcomes and prostatic hypertrophy in older men, there are concerns about its use in eugonadal men without further data to support its use in this setting.

Androgen deprivation therapy

Use of androgen deprivation therapy in the management of men with prostate cancer represents an iatrogenic cause of hypogonadism where restoration of eugonadal status is contraindicated. Androgen deprivation therapy is associated with an increased risk of fracture, with a longer duration of therapy correlating with a higher fracture risk.[19] Significantly, similar to the skeletal effects of glucocorticoids, bone loss may occur rapidly within the first six months of therapy.

As calcium and vitamin D supplementation are likely to be insufficient to prevent bone loss in this setting, some guidelines advocate the early use of antiresorptive therapy if BMD T-score is -2.0 or less in men who have not previously sustained a minimal trauma fracture. Alendronate, risedronate, zoledronic acid and denosumab have all been demonstrated to increase BMD, with the latter also reducing vertebral fractures in men receiving androgen deprivation therapy.

Conclusion

Although osteoporosis in men is underdiagnosed and undertreated, it is also associated with significant morbidity and mortality. It is a major public health problem confronting Australia as the population ages.

Osteoporosis should be considered in men with risk factors for the condition, and treatment considered in those with a high fracture risk. There is now increasing evidence to support the use of various osteoporosis therapies in men. **ET**

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