

Position Statement on the Management of Osteoporosis

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Authors: Ebeling PR, Seeman E, Center J, Chen W, Chiang C, Diamond T, Duque G, Eisman JA, Elliot J, Ganda K, Jesudason D, Jones G, Lyubomirsky G, Major G, Marabani M, March L, Prince RL, Seibel MJ, Stuckey B, Sztal-Mazer S, Stanton S, Waters J and White C.

Background

On 15 March 2019, Osteoporosis Australia (OA) now known as Healthy Bones Australia hosted a National Forum with leading Australian clinical experts to develop a Position Statement on the management of osteoporosis. The purpose of this Position Statement is to provide GPs with clear guidance concerning the identification, investigation and treatment of persons at risk for fragility fractures. Despite the publication of the 2017 RACGP/OA Guidelines '*Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 years of age*' there is persisting under-investigation and under-treatment of patients at risk for fracture, even those with existing minimal trauma fractures. This Position Statement provides an expert opinion-based guidance for osteoporosis management complementing the current 2017 RACGP/OA Guidelines and will be circulated nationally.

Key messaging for GPs

- 1 Osteoporosis is a chronic disease and like other chronic diseases needs long-term treatment over a lifetime in most cases.
- 2 If osteoporosis treatment is interrupted in patients attaining a lower fracture risk, patients must be reviewed with bone density tests, bone remodelling markers and clinical follow-up for new fractures or emerging causes for bone fragility. Bone loss will eventually restart and the benefits of treatment will be lost.
- 3 There is no treatment interruption with denosumab, as its effects are rapidly reversible. If, for whatever reason denosumab treatment cannot be continued, transition to an oral bisphosphonate for at least 12 months is recommended, commencing within 4 weeks of the missed dose.
- 4 In all Australians aged >70 years and in most Australians aged >50 years with a fragility fracture, a bone density test is recommended.
- 5 If a patient has a fracture during treatment this may indicate a need to change therapy, specialist consultation may be required.
- 6 The transition from denosumab to the anabolic drug, teriparatide, may be associated with bone loss.
- 7 A BMD T score ≤ -2.5 is diagnostic of osteoporosis and bone fragility. However, in younger patients with a T score of ≤ -2.5 , the absolute fracture risk may not exceed the intervention threshold.
- 8 As fracture risk also depends on age and other clinical risk factors (e.g. glucocorticoid use) in addition to the BMD T score, an absolute fracture risk calculator (FRAX® or Garvan) is useful to calculate this risk over the next 5 or 10 years. If the 10-year risk of any fragility or hip fracture is >20% or >3%, respectively, treatment is recommended.

General recommendations for management of patients with bone fragility

Osteoporosis is a chronic disease characterised by bone fragility.* Bone fragility predisposes to minimal trauma fractures. Like many common chronic diseases such as diabetes mellitus, hypertension and hyperlipidemia, life-long management with regular review is needed to monitor treatment compliance, efficacy and safety.

In general, treatment of bone fragility should not be stopped because bone mass and microarchitectural deterioration is not reversed using antiresorptive therapy like the bisphosphonates. If treatment is stopped for whatever reason, bone loss will recur leading to a decline in BMD and to an increase in fracture risk. Eventually, any benefits of treatment will be lost. The loss of benefits is very rapid with drugs like denosumab, intermediate with menopausal hormone therapy (MHT) or the orally administered bisphosphonates, and slow with other drugs like zoledronic acid.

For these reasons, stopping treatment is generally not recommended. It is critical to support patients with their adherence to treatment through regular monitoring, education and recall if treatment is ceased for any reason. The panel recommends monitoring for recurrent bone loss assessed by bone densitometry, recurrent fractures and other measures, such as the use of remodelling markers.

When there is uncertainty about an individual patient's benefits and risks in starting or stopping treatment, such as concerns about serious but rare adverse events (such as atypical femoral fracture or osteonecrosis of the jaw), consultation with a specialist is recommended.

Why treat?

The aim of treatment is to reduce the risk of fragility fractures because:

- Fragility fractures increase morbidity, mortality and health care costs.
- Longevity is increasing the numbers of persons aged over 70 years in the community. This is a high-risk group. Over 70% of all fractures occur in women and men over 70 years of age.
- All persons lose bone with advancing age. Bone loss is accelerated in women after the menopause, and in older men due to declining sex hormone levels and reduced physical activity.
- Bone loss reduces the amount of bone and destroys its architecture – the cortical shell thins and becomes porous, trabecular plates thin, perforate and disconnect making the bone fragile.
- There is an urgency to treat patients with prevalent or recent fragility fractures even in patients with osteopenia (the majority of patients with fragility fractures) because the risk of subsequent fractures is increased particularly in the next 12-24 months.
- Hip fractures have the highest morbidity, mortality and cost. These fractures are associated with loss of independence in the majority of cases and high 12-month mortality. However, other major fractures (such as spine and pelvis) are also associated with high morbidity and mortality.
- Most importantly, safe and effective treatments are available that reduce fracture risk in 6-12 months. The choice of therapy must be based on evidence of reduced vertebral, hip and non-vertebral fractures, i.e. all three classes of fragility fractures. As non-vertebral fractures account for 80% of all fractures – only three drugs fulfil this requirement, risedronate, zoledronic acid and denosumab. Alendronate may also achieve this, but the evidence is less compelling.
- Menopausal Hormonal Therapy (MHT) also reduces the risk of vertebral, hip and non-vertebral fractures. The Womens' Health Initiative study demonstrated adverse effects of combined MHT resulted in no net global benefit, but not all beneficial effects of MHT were included. Benefits outweigh risks when MHT is started <60 years of age or within 10 years of menopause and in women with a hysterectomy, implying a negative effect of progesterone. Transdermal oestradiol and new progestogens may also reduce risks of MHT.

*Osteoporosis is defined as a BMD \leq -2.5 SD below the young normal mean. However, in every day usage, the word osteoporosis is commonly used to mean bone fragility. This is a source of confusion. A BMD \leq -2.5 SD does signal the presence of bone fragility, but BMD in the non-osteoporosis range, as occurs in osteopenia (BMD between -2.5 SD and -1 SD) and so-called normal BMD (BMD > 1 SD) does not mean freedom from bone fragility and fracture risk.

Who should be treated?

The decision to treat is determined by the presence of risk factors or diseases associated with bone loss resulting in a high absolute fracture risk. However, the majority of men and women presenting with concern about the possibility of being at risk for fragility fractures may have no underlying risk factors or diseases. The main factor predisposing to bone fragility is advanced age. In persons over 70 years of age the need to treat is high.

In women, menopause with loss of estrogen is the most common cause of bone loss. In men, it is more common to find causes of bone loss such as hypogonadism due to androgen deprivation therapy in men with prostate cancer, primary testicular disease (testicular failure, Klinefelter's disease) or pituitary tumours (such as a prolactinoma), alcohol excess and other causes of secondary osteoporosis.

The importance of an existing fracture:

Irrespective of the category of BMD such as osteopenia (BMD T score between -2.5 and -1 SD) or osteoporosis (BMD T score \leq -2.5 SD), an existing or recent hip, vertebral or non-vertebral fracture signals the presence of bone fragility and the risk for further fractures within 12 months, and so should result in urgent investigation and treatment.

Risk factors: In line with the 2017 RACGP/OA Guidelines, Figures 1 and 2 flow charts are current for risk factors. However, in individuals treated with glucocorticoids, or aromatase inhibitor therapy or androgen deprivation therapy, the threshold for intervention is at a higher T score (-1.5 and -2.0, respectively).

Figure 1

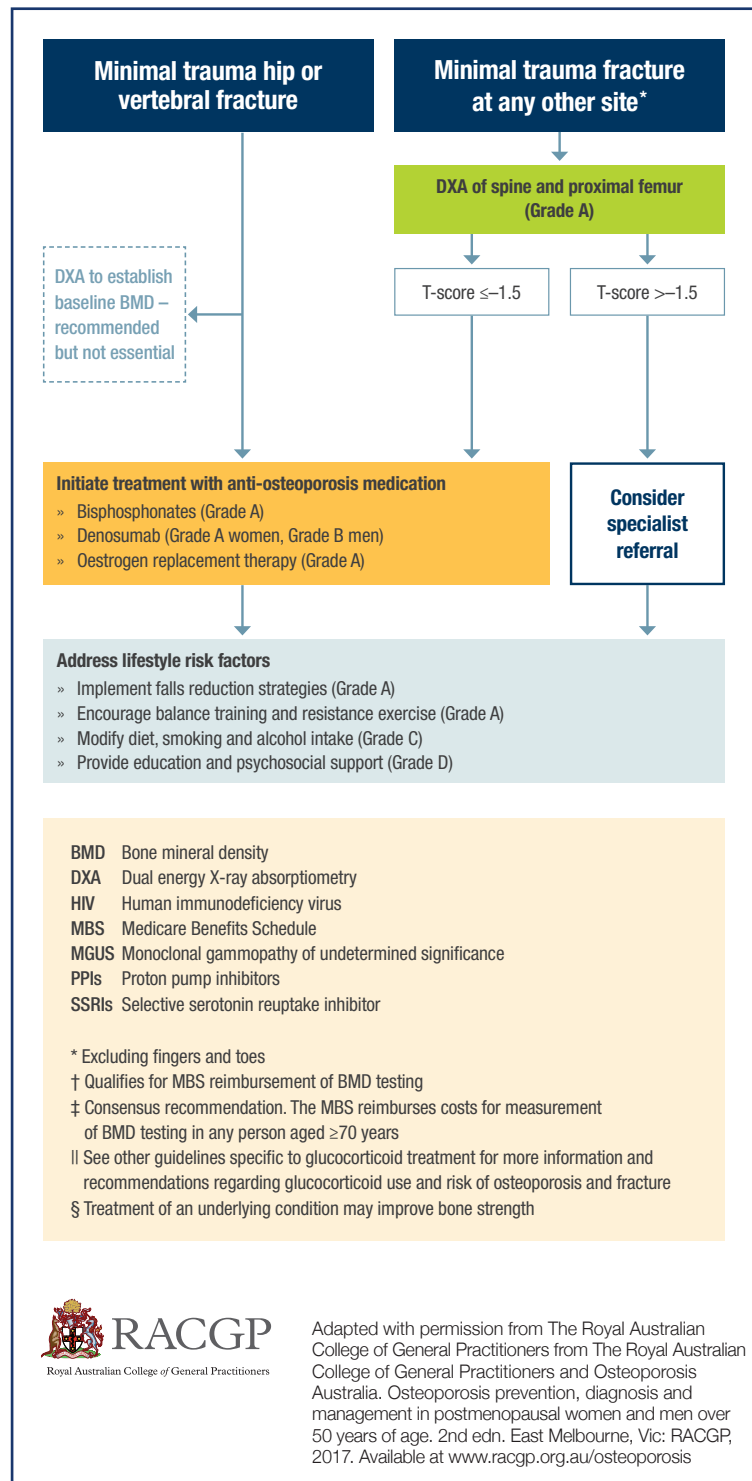
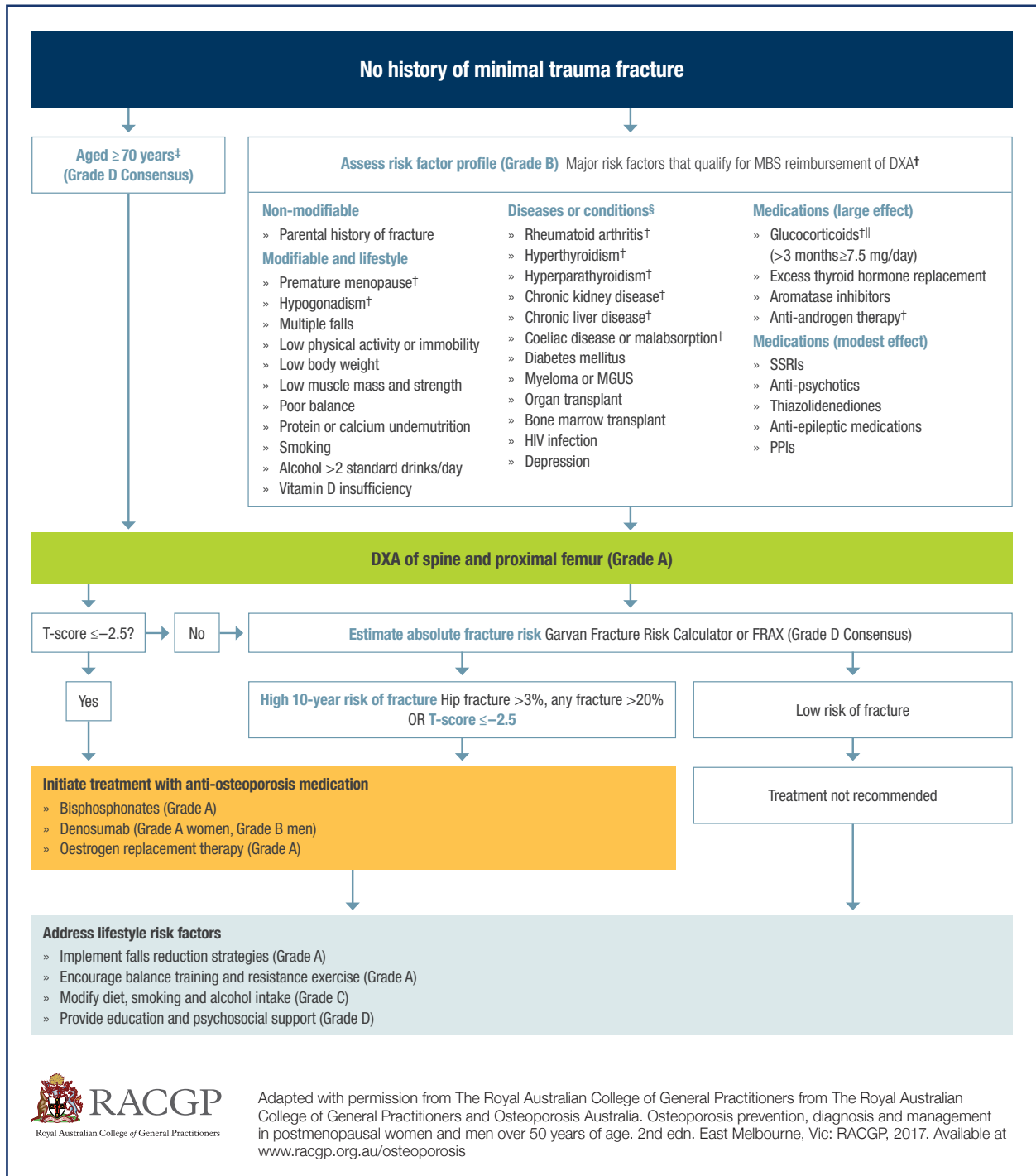


Figure 2



Investigations

Initial investigations: FBE, U&Es, serum protein electrophoresis, serum free light chains/urine Bence Jones protein, LFTs, Ca, PO₄, 25(OH) vitamin D, PTH, TSH, ESR/CRP and testosterone (in males only).

Further investigations as required: Coeliac screen, E₂, LH and FSH in women if premature menopause is suspected, hypercortisolism screen, 24-hour urine calcium and creatinine excretion.

Measurement of BMD: Measurement of BMD is appropriate because the lower the BMD, the higher the risk for fracture and the greater the need for prompt treatment. A BMD T score ≤ -2.5 SD signals a high risk for fracture and so is designated as a diagnostic threshold of ‘osteoporosis.’

However, patients with osteopenia, with BMD better than -2.5 SD, (i.e., between -2.5 and -1.0 SD) does NOT necessarily signal freedom from bone fragility, freedom from the risk of fracture or freedom from the need for treatment. Fracture risk is lower than in persons with osteoporosis, but the risk is still significant.

If a fracture is present and the patient has osteopenia, this fracture is still likely to be a fragility fracture and the patient requires treatment. Assessment of patients with osteopenia but without fractures, in collaboration with a specialist may be advisable as bone fragility is often increased. This may be due to deterioration of bone microarchitecture not captured by the BMD measurement.

As presented in the 2017 RACGP/OA Guidelines, absolute fracture risk should be assessed using a combination of clinical risk factors and BMD in patients without a fragility fracture using either the FRAX® or Garvan fracture risk calculators. Other risk factors, including measurement of bone remodelling markers should be assessed as aids to decision making and, if necessary, discussed with a specialist.

Follow-up BMD scans by DXA are important to monitor treatment responses and may be appropriate to reassure the patient. However, repeat measurement should not be done more often than 2 yearly, except in cases of anticipated rapid bone loss (post-transplant, glucocorticoid use), or a change in therapy when the scan may be repeated after 12 months. A precision error of 1-4% must be taken into account when interpreting changes in bone density. Results of BMD scans obtained at shorter intervals (e.g. yearly) need to be interpreted with caution as changes in bone density are often within the margin of the precision error.

Which drug?

The choice of the first-line anti-resorptive pharmacological therapeutic agent is based on the quality of evidence of efficacy and safety. Three drugs fulfil the requirement of evidence for reduction in spine, hip and non-vertebral fractures – risedronate, zoledronic acid and denosumab. Alendronate reduces vertebral and hip fractures, but the evidence for non-vertebral fracture risk reduction is less robust. Bisphosphonates (risedronate, zoledronic acid and alendronate) and denosumab are first-line therapeutic options.

Anti-resorptive therapy reduces the risk of vertebral and hip fractures by 40-70% and non-vertebral fractures by 20-30%. The five following alternatives are evidence-based. The choice of agent is based not on greater efficacy, but on personal preference, convenience and factors specific to each drug, as discussed below.

For the majority of patients who have sustained a fragility fracture or are over the age of 70 and have low bone mineral density, the benefits of therapy in reducing risk of fracture should strongly outweigh the risks of rare adverse events such as osteonecrosis of the jaw or atypical femur fractures that may be associated with long-term therapy.

Types of antiresorptive drugs:

- 1 Oral bisphosphonates (alendronate and risedronate):** Regular review and assessment with long-term use of oral bisphosphonates is required to monitor compliance, occurrence of fractures despite treatment, and side effects. Monitoring of BMD should be done no more often than 2-yearly because changes at one year are usually small and may not differ from the measurement error. Enteric coated risedronate has the advantage of a lower risk of upper gastrointestinal irritation, and can be taken in the morning either with or without food.
- 2 Zoledronic acid:** Annual infusions with 5 mg of zoledronic acid is recommended for 3 years. Infusions given less often, e.g. every 18 months, also reduce the risk of fragility fractures in women with osteopenia. Monitoring is recommended with repeat BMD no more than 2-yearly.
- 3 Denosumab:** Treatment using Denosumab is by 6-monthly subcutaneous injections. Six monthly treatment intervals must be rigorously followed, because if treatment is delayed, or ceased, bone loss may recur very quickly. This may subsequently result in a return of BMD to pre-treatment levels within 12 months. If the delay following a denosumab injection is more than 6 months, organise the next injection as soon as practical to restore the regularity of 6 monthly administration. This should occur preferably within a window 4-6 weeks following the missed injection. If there is a good reason to stop denosumab (such as an adverse reaction) it is recommended to commence oral bisphosphonate therapy immediately to reduce the risk of a rapid decrease in BMD, and the resultant increased risk of vertebral fractures.

- 4 **SERMS:** SERMs are an option to be considered for treatment in early/post-menopausal women. However, there is no evidence for prevention and reduction of non-vertebral and hip fractures. SERMs may be indicated in women with spinal osteoporosis and a past or family history of breast cancer.
- 5 **Menopause hormonal treatment (MHT):** Hormonal therapy remains an option for young post-menopausal women, if initiated within 10 years of menopause or < 60 years of age, particularly with troublesome symptoms of menopause.

Fracture despite first-line therapy

Treatments significantly reduce fracture risk but do not completely eliminate fracture risk. For patients who fracture during anti-resorptive treatment, ‘treatment failure’ is defined by the occurrence of ≥ 2 fragility fractures during anti-resorptive therapy (or one fracture with a deterioration in BMD) for more than 12 months, and this should trigger a specialist referral for consideration of anabolic therapy. One fracture after more than 12 months of anti-resorptive therapy may also lead to consideration of anabolic therapy, especially if the patient has sustained a fracture prior to commencing treatment. It is recommended to administer anabolic therapy (teriparatide or romosozumab) for 18 months to two years or one year, respectively, then this should be promptly followed by an anti-resorptive agent. In general, a specialist referral is recommended in such cases to assess use and prescription of anabolic drugs.

Teriparatide

This anabolic therapy is currently initiated by specialists only in severe cases of bone fragility when incident fractures occur despite anti-resorptive therapy. It is self-administered as a daily subcutaneous injection. There is evidence of greater antifracture efficacy with teriparatide than oral risedronate. In some situations, therapy with teriparatide may be appropriate (e.g. multiple fractures or very low bone density) as a first-line treatment, but this dosing regimen is currently not PBAC approved in Australia. Combining specific anti-resorptive (zoledronic acid, denosumab) with teriparatide therapy may be advantageous, but evidence of superior antifracture efficacy of combined anabolic plus anti-resorptive therapy over either agent alone is currently lacking and only one PBS-reimbursed treatment is allowed. The sequence of denosumab followed by teriparatide (after stopping denosumab) may be associated with transient bone loss, particularly at the hip, and is not recommended. It is imperative to promptly commence an anti-resorptive agent after teriparatide therapy has been completed to maintain the accrued benefits of teriparatide.

Romosozumab

Romosozumab is a “targeted therapy” for treatment of osteoporosis that inhibits an inhibitor of bone formation. It is the most recent pharmacologic therapeutic addition for osteoporosis. It is a monoclonal antibody which is a potent bone anabolic agent (builds new bone). Unlike teriparatide, which predominantly increases bone formation, romosozumab has a unique dual action to both increase bone formation and reduce bone resorption. This mode of action leads to a marked increase in BMD, greater than what is seen with oral alendronate or teriparatide.^{1,2} It can only be prescribed by specialists and administered by a specialist or GP as a subcutaneous injection (2x injections once a month). It is restricted for use in severe osteoporosis in patients with at least 2 fractures and low bone density. After 12 months of romosozumab therapy, there is a statistically significant reduction in vertebral fracture and a trend towards reduction in non-vertebral fractures in post-menopausal women with osteoporosis at high risk for fracture, and has greater antifracture efficacy to oral alendronate.^{3,4} At 24 months, using sequential therapy of romosozumab followed by anti-resorptive therapy, there is a statistically significant reduction in all types of fracture (vertebral, hip and non-vertebral fracture). This highlights the imperative to promptly commence an anti-resorptive agent after romosozumab therapy has been completed to maintain the accrued benefits of romosozumab and achieve the best outcomes. While fracture reduction data in men is lacking, romosozumab is effective in increasing BMD and appears safe in men with osteoporosis.⁵ In one trial, the risk of cardiovascular events was numerically increased,⁴ so romosozumab should not be used in patients with an acute myocardial infarct or stroke in the preceding 12 months.

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How long should treatment be given?

If treatment is initiated, for the majority of patients it should be permanent (lifelong) because:

- Any antiresorptive therapy slows, but does not reverse, the destruction of bones.
- Stopping treatment results in recurrence of bone loss particularly following cessation of denosumab with the rare occurrence of multiple vertebral fractures in a minority of patients.
- If treatment is stopped, inform patients that bone loss will recur. Ongoing monitoring of patients is critical following treatment cessation.

Adverse events

Anti-resorptive agents are safe; the benefits of treatment greatly outweigh the risks. The incidence of atypical femur fractures (AFF) and osteonecrosis of the jaw (ONJ) is exceedingly low, a fact that is not well appreciated by patients and therefore requires discussion as it is a source of concern for many. However, any invasive dental procedures required (extractions, implants) should be performed prior to initiation of antiresorptive treatment. Once commenced, it is not recommended to interrupt antiresorptive treatment for invasive dental procedures. Both AFF and ONJ may be treated using anabolic therapy like teriparatide, although high level evidence is lacking at this stage. Specialist advice should be sought regarding osteoporosis treatment in patients who have AFF or ONJ. Teriparatide is safe and has not been shown to be associated with osteosarcoma in humans. Although cardiovascular events such as myocardial infarction and stroke have been identified in some but not all trials with romosozumab, it is currently unclear whether their incidence is increased by romosozumab or whether the findings are due to chance alone or a decrease in incidence with alendronate. However, romosozumab should not be used in patients who have had a myocardial infarction or stroke in the last 12 months. Currently other newer anabolic agents like abaloparatide remain unavailable for prescription in Australia.

Position on the role of exercise, calcium and vitamin D in osteoporosis

Calcium and vitamin D

Encourage sufficient intake of calcium containing food and ensure vitamin D levels are above a serum 25(OH) D level of 50 nmol/L. Recommendations are 1,000mg calcium daily (for adults generally) increasing to 1,300 mg (for women >50 and men >70 on osteoporosis treatments) with supplements if required of 500-600mg daily.

Exercise

Avoid immobilisation and daily weight-bearing exercise is encouraged. Moderate to high intensity progressive resistance and impact training increases bone density, maintains muscle mass and strength, and mobility to reduce falls. A recent Cochrane Review showed exercise reduced the rate of falls in older adults by 23%, and the number of individuals with fractures by 27%, with a trend to a decrease in fractures.

Bone remodelling markers

Expert opinion is divided on recommendations for GPs to use bone turnover markers. Internationally recommended markers are C-terminal telopeptide of type 1 collagen (CTX) for bone resorption, and amino-terminal propeptide of type 1 collagen (PINP) for bone formation. Concerned GPs are advised to consult a specialist to discuss the appropriate role of bone turnover markers. However, their most important role is in measuring short-term (3-month) responses to oral bisphosphonates and anabolic drugs. In this regard, CTX is reimbursed under Medicare for GP use in patients with osteoporosis (one test per year).

Author details

Professor Peter Ebeling AO: Endocrinologist, Head of Department of Medicine, Monash University, Medical Director, Healthy Bones Australia and Board Member International Osteoporosis Foundation

Professor Ego Seeman AM: Endocrinologist, Austin Repatriation Hospital, Victoria and Board Member International Osteoporosis Foundation

Professor Jacqueline Center: Endocrinologist, Deputy Director, Department of Endocrinology St Vincent's Hospital Sydney, Conjoint Professor of Medicine, University of NSW and Senior Research Fellow Garvan Medical Institute of Medical Research

Dr Weiwen Chen: Endocrinologist, St Vincent's Hospital Sydney and Research Officer Garvan Medical Institute of Medical Research, NSW

Dr Cherie Chiang: Endocrinologist and Pathologist Royal Melbourne and Alfred Hospital, Victoria

A/Professor Terry Diamond: Endocrinologist, St George Private Hospital, NSW

Professor Gustavo Duque: Geriatrician, Chair of Medicine, Western Health, Director Australian Institute for Musculoskeletal Science (AIMSS), Melbourne University and Immediate Past President of the Australian and New Zealand Society for Sarcopenia and Frailty Research

Professor John Eisman AO: Endocrinologist, St Vincent's Hospital Sydney, Laboratory Head - Osteoporosis and Translational Research Garvan Institute of Medical Research and Conjoint Professor of Medicine, University of NSW

Dr Kirtan Ganda: Endocrinologist, Sydney Concord Hospital, NSW

Dr Jane Elliot: GP, North Adelaide Family Practice, South Australia

Dr David Jesudason: Endocrinologist, Director of Endocrinology, The Queen Elizabeth Hospital, South Australia

Professor Graeme Jones: Rheumatologist and Head of Musculoskeletal Research Group, Menzies Institute of Medical Research, University of Tasmania

Greg Lyubomirsky: CEO, Healthy Bones Australia

Dr Gabor Major: Rheumatologist, Newcastle John Hunter Hospital, NSW

Dr Mona Marabani: Rheumatologist, Head Department of Medicine, Canterbury Hospital, NSW and Emeritus Director Arthritis Australia

Professor Lyn March AM: Rheumatologist, Royal North Shore Hospital, School of Medicine, University of Sydney and Representative of the Fragility Fracture Network (FFN)

Professor Richard Prince: Endocrinologist, School of Medicine and Pharmacy, University of Western Australia and Chair Therapeutics Committee, Australian and New Zealand Bone and Mineral Society

Professor Markus J Seibel: Endocrinologist, The University of Sydney, Concord Repatriation General Hospital and Chair, SOS Fracture Alliance

Professor Bronwyn Stuckey: Endocrinologist, Medical Director Keogh Institute for Medical Research Sir Charles Gairdner Hospital, Clinical Professor School of Medicine and Pharmacology University of Western Australia and Past President Australasian Menopause Society

Dr Shoshana Sztal-Mazer: Endocrinologist, Alfred Health, Victoria

Dr Sonia Stanton: Endocrinologist, ACT Canberra Hospital and Health Service

A/Professor Justine Waters: Public Health Adviser Healthy Bones Australia and Adjunct Associate Professor, University Technology Sydney, NSW

A/Professor Chris White: Endocrinologist, Department of Clinical Chemistry and Endocrinology, Prince of Wales Hospital. Director, Research at South Eastern Sydney Local Health District and Cojoint Associate Professor of Medicine at University of NSW

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