RACGP
Royal Australian College of General Practitioners

HEALTHY BONES AUSTRALIA

Osteoporosis management and fracture prevention in postmenopausal women and men over 50 years of age

March 2024

Executive Summary

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This guide is an evidence update of the *Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 years of age*, second edition, published in 2017 by The Royal Australian College of General Practitioners (RACGP).[1] The accumulation of high-quality evidence supporting changes to clinical practice over the past five years, the need for expert consensus and opinion, and new developments in the pharmacological management of osteoporosis, especially the role of osteoanabolic therapies, prompted this revision.

Purpose

This guide is designed to provide clear, evidence-based recommendations to assist Australian general practitioners (GPs) in managing patients over 50 years of age with poor bone health, including osteopenia and osteoporosis. Its purpose is to support clinical judgement making in the individual patient, not to replace it, and help busy GPs achieve better patient outcomes by the:

- prevention of first fracture
- early diagnosis of osteoporosis to allow prompt bone health management
- identification of undiagnosed patients following a first fracture to prevent subsequent fractures
- management of secondary causes of poor bone health.

Scope

This guide provides evidence-based recommendations, content and statements across key topics constituting best practice in the identification, diagnosis, prevention and treatment of osteoporosis.

Most recommendations in the previous (second) edition were based on critical analysis of published, peer-reviewed evidence from 2006 to 2016, following a systematic review of available evidence. Every section in this new edition has been reviewed and updated with current peer-reviewed evidence by a bone expert with particular subspeciality expertise in that topic. Focused literature searches were also undertaken in subject areas that the Guideline Review Committee felt needed particular attention. These included fracture risk assessment tools, the frequency of dual energy X-ray absorptiometry (DXA) monitoring, patients at ‘imminent’ or ‘very high’ fracture risk and pharmacological therapies. Where there was insufficient evidence available, or where the quality of the evidence did not meet minimum requirements (as described in **Appendix A**), recommendations were developed through Guideline Review Committee consensus cognisant of the complexities and time constraints of a busy GP. Details on the development process, how to use this guide and membership of the Guideline Review Committee are found in **Appendices A, B** and **D**.

What's New?

Certain areas of osteoporosis management have evolved significantly since the second edition. Specifically, recommendations for the use of fracture risk assessment tools, particularly FRAX®, for screening, the risk of rebound vertebral fracture following denosumab cessation, the removal of strontium as a therapy, the clarification of 'imminent' or 'very high' fracture risk in patients, the importance of calcium and vitamin D status and the use of osteoanabolic therapies deserved special attention. A 'Special issues' section addresses updated recommendations on delayed dental healing and the management of bone health in patients undergoing androgen deprivation therapy for prostate cancer or aromatase inhibitor treatment for breast cancer.

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References

1. The Royal Australian College of General Practitioners. Osteoporosis prevention, diagnosis and management post-menopausal women and men over 50 years of age. 2nd edn. South Melbourne, Vic: RACGP, 2017.

Summary of recommendations

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*Recommendations underwent a focused and detailed published literature search during which multiple databases were interrogated to identify publications subsequent to the previous edition (ie since 2016). Refer to **Appendix B** for a full explanation.

These were then reviewed by a subject matter adviser (see **Appendix D**) with subspeciality expertise in the topic and the relevant chapter(s) updated. The final draft of the chapter(s) underpinning relevant recommendation(s) was then reviewed by the National Osteoporosis Guideline Review Committee (see **Appendix D)** and discussed at several face-to-face and online meetings.

All other recommendations have been updated by at least one subject matter adviser with subspeciality expertise in the area and reviewed by the National Osteoporosis Guideline Review Committee at two face-to-face meetings.

1: Risk factors, fracture risk assessment and case-finding

Section	No.	Recommendation	Grade
1.1 Identifying patients to investigate for osteoporosis	1	All individuals over the age of 50 years who sustain a fracture following minimal trauma (such as a fall from standing height, or less) should be considered to have a presumptive diagnosis of osteoporosis.	A
	2 *	Conduct a clinical risk factor assessment in postmenopausal women and men over the age of 50 years with one or more major risk factors for minimal trauma fracture to guide bone mineral density (BMD) measurement and prompt timely referral and/or drug treatment.	A

	3	A presumptive diagnosis of osteoporosis can be made in a patient with a vertebral fracture or hip fracture in whom there is no history of significant trauma. Caution regarding diagnosis and treatment should be exercised if only a single mild vertebral deformity (height loss) is detected, especially in a patient under the age of 60 years.	B
1.2 Measurement of bone mineral density	4 *	Measure BMD by dual energy X-ray absorptiometry (DXA) scanning on at least two skeletal sites, including the lumbar spine and hip, unless these sites are unsuitable (eg hip prosthesis).	A
1.3 Assessment of absolute fracture risk	5 *	Assessment of absolute fracture risk, using the Fracture Risk Assessment Tool (FRAX®; https://fraxplus.org (https://fraxplus.org)) may be useful in assessing the need for treatment in individuals who do not clearly fit established criteria.	B
	6 *	Patients with a very high and/or imminent fracture risk should be promptly referred to a specialist for consideration of osteoanabolic therapy as first-line treatment.	C
1.4 Case-finding	7	Those aged >50 years with a current or prior minimal trauma fracture should be assessed and appropriately treated.	A
	8 *	For those aged >50 years with lifestyle and non-modifiable risk factors (eg parent with hip fracture), use FRAX® to calculate absolute fracture risk. When FRAX® risk for major osteoporotic fracture (MOF) is ≥10%, refer for DXA. If the risk of MOF is <10%, DXA is not recommended. Re-stratify risk with FRAX® after DXA using BMD reading and treat when: • BMD T-score is ≤−2.5 • BMD T-score is between −1.5 and −2.5 and the FRAX® risk for MOF is ≥20% and/or the hip fracture risk is ≥3%.	D

	9 *	For those aged >50 years with diseases/chronic conditions/ medications associated with increased fracture risk, refer for BMD assessment by DXA. Re-stratify risk with FRAX® after DXA using BMD reading and treat when: • BMD T-score is ≤−2.5 • BMD T-score is between −1.5 and −2.5 and the FRAX® risk for MOF is ≥20% and/or the hip fracture risk is ≥3%.	C
	10	There is insufficient evidence to recommend population-based systematic screening with BMD measurement for reduction of osteoporotic fractures in Australia, and case finding is recommended.	B

2: General bone health maintenance and fracture prevention

Section	No.	Recommendation	Grade
2.1 Calcium, protein, and vitamin D	11 *	**For generally healthy older people:** Although the absolute benefit of calcium and vitamin D supplements in short-term (less than six years) studies for fracture reduction is low, there is good evidence that adequate calcium intake and vitamin D status are important for long-term maintenance of bone and muscle function.	C
	12 *	**For frail and institutionalised older people:** Calcium and vitamin D supplementation, together with adequate protein intake, are recommended for fracture prevention. Optimisation of calcium and vitamin D should be the standard of care for this group of people.	B
	13 *	**For people taking osteoporosis treatments:** • Calcium supplements should be recommended if their dietary calcium intake is less than 1300 mg per day. • Vitamin D supplements should be recommended to correct low serum vitamin D levels (25-hydroxyvitamin D <50 nmol/L).	C

	14 *	For most people with olive or pale brown skin, no other risk factors and who are at intermediate risk of skin cancer, a few minutes of sunlight exposure towards the middle of the day, with time depending on latitude, season and skin area exposed, followed by further sun protection measures should maintain vitamin D levels. People with dark skin at low risk of skin cancer have less need for sun protection, but require more time outdoors to avoid vitamin D deficiency. People at high risk of skin cancer need sun protection most of the year, which may limit vitamin D synthesis. The use of sunscreen, in practice, does not greatly affect vitamin D status.	B
2.2 Reducing falls	15	Opportunistic case finding should be undertaken as per the recommended algorithm[1] to identify older people at risk of falls and fall-related injury.	A
	16	Offer further assessment and/or interventions to prevent falls based on the level of risk identified.	A
2.3 Exercise	17	**Exercises recommended to reduce fracture risk:** • Muscle resistance (strength) training should be regular (at least twice a week), moderate–vigorous and progressive. • Weight-bearing impact exercises should be performed most days (at least 50 moderate impacts) and include moderate-to-high loads in a variety of movements in different directions. • Balance training activities should be challenging. Limit prolonged sitting (sedentary behaviour).	B
	18	Exercise programs for very frail older institutionalised people and those with a high vertebral fracture risk should be supervised, modified and tailored to minimise the potential to increase the risk of falls, injury and vertebral fractures.	C
	19	Prescribe extended and supervised exercise therapy, including targeted resistance and challenging balance training, after hip fracture to improve mobility, strength and physical performance and to reduce falls risk.	B

	20	Evidence for the benefits of exercise after vertebral and non-hip fractures is limited, but suggests supervised resistance training will build bone once a fracture has healed to the same extent as in non-fractured patients. For people with a vertebral fracture, exercises to strengthen back muscles, enhance flexibility and improve posture, as well as to reduce falls risk, should be considered.	D

3: Pharmacologic approaches to prevention and treatment

Section	No.	Recommendation	Grade
3.1 Bisphosphonates	21 *	Bisphosphonate therapy (alendronate, risedronate or zoledronate) should be considered for the primary prevention of vertebral fractures in women with osteopenia who are at least 10 years postmenopause.	B
	22 *	Bisphosphonate therapy is recommended for reducing the risk of vertebral and non-vertebral fractures in postmenopausal women and men over the age of 50 years at high risk of fracture (those with osteoporosis by BMD criteria, or prior minimal trauma fracture).	A (women) C (men)
	23 *	Reconsider the need to continue bisphosphonate therapy after 5–10 years in postmenopausal women and men over the age of 50 years with osteoporosis who have responded well to treatment (T-score ≥−2.5 and no recent fractures). If BMD remains low (T-score ≤−2.5) and/or there are incident fragility fractures, continue treatment. Treatment should be restarted if there is bone loss, especially at the hip, or if a further minimal trauma fracture is sustained.	D
3.2 Denosumab	24 *	Denosumab is recommended for the treatment of osteoporosis in postmenopausal women at high risk of minimal trauma fracture.	A
	25 *	Denosumab may be considered as an alternative to bisphosphonates for the treatment of men at increased risk of minimal trauma fracture.	B

	26 *	Denosumab therapy should not be interrupted. If denosumab needs to be ceased, patients should be transitioned to bisphosphonate therapy for a minimum of 12 months.	C
3.3 Romosozumab	27 *	Romosozumab is recommended as first-line therapy for osteoporosis treatment in postmenopausal women at very high risk of minimal trauma fracture.	A
	28 *	Romosozumab is recommended as first-line therapy for osteoporosis treatment in men at very high risk of minimal trauma fracture.	C
3.4 Menopausal hormone therapy	29 *	Consider oestrogen replacement therapy to reduce the risk of fragility fractures in postmenopausal women within 10 years of menopause. The increased risk of adverse events associated with treatment should be carefully weighed against benefits.	A
	30 *	Selective oestrogen receptor modulators (SERMs) should be considered as a treatment option for postmenopausal women with osteoporosis where vertebral fractures are the major osteoporosis risk (based on low spine BMD and/or an existing vertebral fracture) and where other agents are poorly tolerated. SERMs may be particularly useful in younger postmenopausal women at risk of vertebral fracture with a prior or family history of breast cancer.	A
3.5 Recombinant human parathyroid hormone	31	Recombinant human parathyroid hormone (teriparatide) treatment is recommended to reduce fracture risk in postmenopausal women with osteoporosis who have sustained a subsequent fracture while on antiresorptive therapy, or in those at very high fracture risk.	A
	32	Recombinant human parathyroid hormone (teriparatide) treatment is recommended to reduce fracture risk in men aged over 50 years with osteoporosis who have sustained a subsequent fracture while on antiresorptive therapy, or in those at very high fracture risk.	C

4: Ongoing monitoring

Section	No.	Recommendation	Grade

4.1 Ongoing monitoring	33	Regularly reassess fracture risk and the requirement for anti-osteoporotic therapy in patients not receiving therapy, but who remain at increased fracture risk.	C
	34	Clinically review all patients 3–6 months after initiating pharmacological therapy for osteoporosis, and 6–12 monthly thereafter for medication side effects and therapy adherence.	C
	35	Measurement of bone turnover markers should be confined to specialist practice. Measurement of bone turnover markers may be useful for monitoring medication adherence and efficacy and for evaluation of secondary causes of bone loss.	D

5: Special issues

Section	No.	Recommendation	Grade
5.1 Management of osteoporosis in frail and older people (over 75 years of age)	36	Consider a multifactorial approach (environment, pharmacological treatments, exercise, nutrition) to reduce falls and fracture risk.	C
5.2 Bone loss associated with aromatase inhibitor therapy for breast cancer and androgen deprivation therapy for prostate cancer	37	All women commencing aromatase inhibitor therapy should have baseline assessment of fracture risk prior to commencing therapy, including clinical risk factors, biochemistry and BMD (DXA) measurement, with ongoing monitoring based on risk factors.	A
	38	Women commencing aromatase inhibitor therapy who fall within one of the following two categories should commence antiresorptive therapy unless contraindicated: • age ≥70 years with BMD T-score ≤–2.0 • age >50 years with a minimal trauma fracture (including radiological vertebral fracture) or a high estimated 10-year fracture risk. There is limited evidence specific to women receiving aromatase inhibitors to guide firm recommendations outside these criteria, especially in premenopausal women.	A

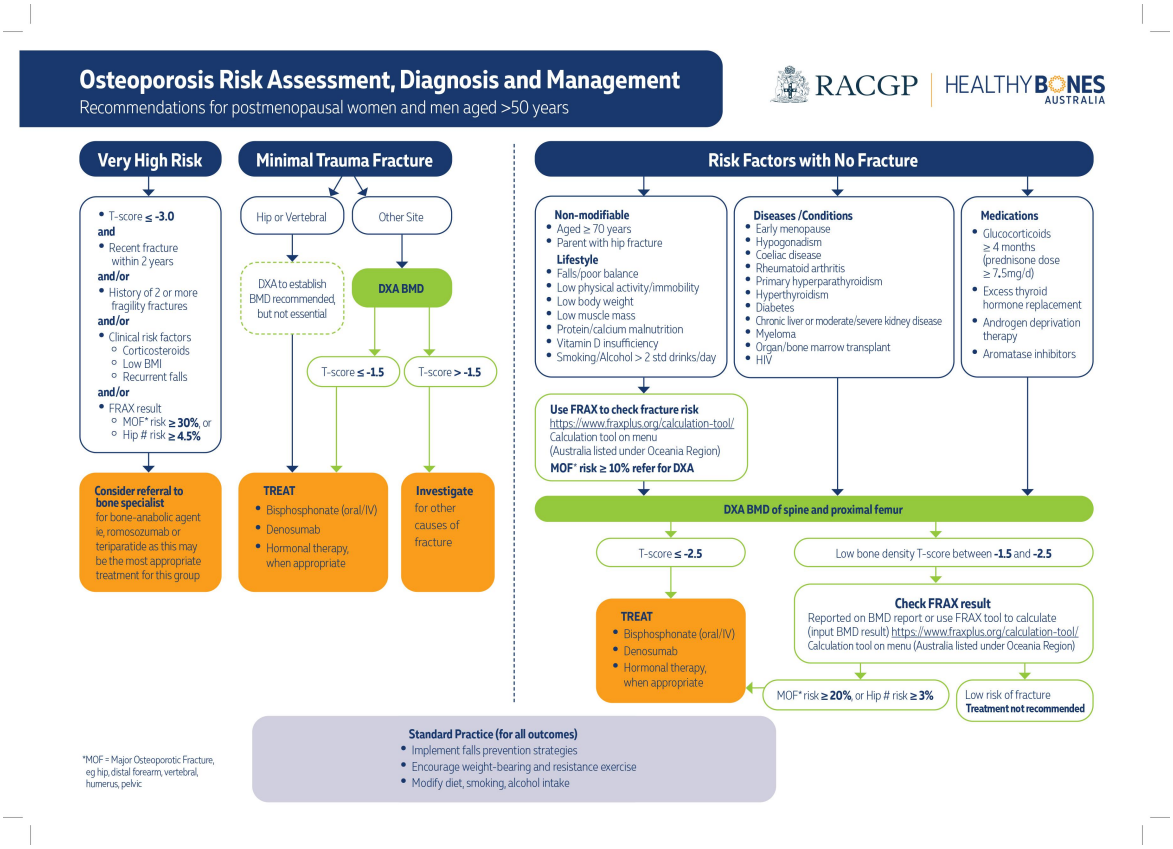
	39	The duration of antiresorptive treatment in women undergoing, or who have completed, aromatase inhibitor therapy should be individualised and based on absolute fracture risk.	D
	40	General measures to prevent bone loss should be implemented in all women commencing aromatase inhibitor therapy.	C
	41	All men commencing androgen deprivation therapy (ADT) should have a baseline assessment of fracture risk, including BMD assessment by DXA.	A
	42	All men receiving ADT with a history of minimal trauma fracture should be commenced on antiresorptive therapy, unless contraindicated.	A
	43	Bone health should be reviewed 1–2 yearly in men on continuous ADT.	C
	44	General measures to prevent bone loss should be implemented in all men commencing ADT.	C
5.3 Medication-related osteonecrosis of the jaw (MRONJ)	45 *	MRONJ is a rare complication of osteoporosis therapy and most patients will not be at increased risk of MRONJ. Consider patient risk of MRONJ prior to starting osteoporosis therapy and ensure high-risk patients receive dental review prior to therapy initiation. Given the long *in vivo* half-life of bisphosphonates, there is little benefit to their cessation prior to dental extraction. Invasive dental procedures in patients on denosumab should be performed just prior to the next six-monthly injection because the *in vivo* effect on bone suppression will be waning.	C

Reference

1. Montero-Odasso M, van der Velde N, Martin FC, et al. World guidelines for falls prevention and management for older adults: a global initiative. Age Ageing 2022;51(9):afac205. doi: 10.1093/ageing/afac205.

Osteoporosis risk assessment, diagnosis and management flow chart

Osteoporosis risk assessment, diagnosis and management flow chart



Osteoporosis risk assessment, diagnosis and management flow chart

Acronyms

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25(OH)D	25-Hydroxyvitamin D
ADT	Androgen deprivation therapy
AFF	Atypical fracture of the femur
AI	Aromatase inhibitor
ARR	Absolute risk reduction
BMD	Bone mineral density
BMI	Body mass index
CEE	Conjugated equine (o)estrogen
CI	Confidence interval
DXA	Dual energy X-ray absorptiometry
ER	(O)Estrogen receptor
FLS	Fracture liaison service
FN	Femoral neck
FRAX®	Fracture Risk Assessment Tool
GIT	Gastrointestinal tract
GnRH	Gonadotropin-releasing hormone
GP	General practitioner
HIV	Human immunodeficiency virus
hPTH	Human parathyroid hormone

HR	Hazard ratio
IV	Intravenous
MBS	Medicare Benefit Schedule
MHT	Menopausal hormone therapy
MOF	Major osteoporotic fracture
MRONJ	Medication-related osteonecrosis of the jaw
NHMRC	National Health and Medical Research Council
NNT	Number needed to treat
NSW	New South Wales
OR	Odds ratio
PBS	Pharmaceutical Benefits Scheme
PINP	Procollagen type 1 amino-terminal propeptide
PTH	Parathyroid hormone
QALY	Quality-adjusted life year
QCT	Quantitative computed tomography
RACGP	The Royal Australian College of General Practitioners
RANKL	Receptor activator of nuclear factor kappa B ligand
RaR	Rate ratio
RCT	Randomised controlled trial
RDI	Recommended dietary intake
RR	Relative risk
SD	Standard deviation
SE	Summary estimate

SERMs	Selective (o)estrogen receptor modulators
SFP	Secondary fracture prevention
WHI	Women’s Health Initiative
WHO	World Health Organization

Background

Background

Definition

Osteoporosis is characterised by both low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, leading to decreased bone strength, increased bone fragility and a consequent increase in fracture risk. Osteoporotic fractures usually follow falls from a standing height or less in individuals with decreased bone strength. BMD can be reliably measured by scanning of the skeleton using dual energy X-ray absorptiometry (DXA).

BMD is usually reported as a T-score, the number of standard deviations (SDs) of BMD measurement above or below that of young healthy adults of the same sex. The World Health Organization (WHO) has defined osteoporosis and osteopenia based on T-score (**Table 1**).[1] Although Australia's Pharmaceutical Benefits Scheme (PBS) uses the WHO T-score range for osteoporosis to determine eligibility for subsidy on osteoporosis medications, it is important to note that BMD is only one of several factors that contributes to an individual's fracture risk. Because osteopenia and normal BMD are much more common than osteoporosis, approximately 50% of first or subsequent minimal trauma fractures (trauma equivalent to a fall from standing height or less) occur in people with T-scores in the normal or osteopenic range.[2–5] **These people should still be considered at increased risk of subsequent fracture** because fracture contributes to subsequent fracture risk independent of BMD.[6]

Table 1. WHO definitions of osteoporosis and osteopenia[1]

Normal BMD	T-score –1.0 or above	BMD not more than 1.0 SD below young adult mean
Osteopenia	T-score between –1.0 and –2.5	BMD between 1.0 and 2.5 SDs below young adult mean
Osteoporosis	T-score –2.5 or below	BMD 2.5 or more SDs below young adult mean

Clinical symptoms

Osteoporosis is a 'silent disease' because deterioration of skeletal tissue proceeds with no symptoms until a symptomatic fracture occurs, and thus the condition is under-recognised and affected individuals are undertreated.[4–9]

Vertebral fractures may be asymptomatic or present with acute, usually self-limiting back pain. However, subclinical fractures are important predictors of future fracture risk, particularly for vertebral fractures.[10,11]

More commonly, vertebral fractures are associated with gradual height loss resulting in increasing thoracic kyphosis and back pain. Non-vertebral or peripheral fractures usually present with more obvious fracture symptoms following a fall, although stress fractures may present as acute regional musculoskeletal pain.

Burden of osteoporosis and fractures in Australia

A 2012 burden of disease analysis report estimated that, in 2022, 6.2 million Australians aged >50 years would have osteoporosis or osteopenia, an increase of 31% from 2012.[12] This modelling predicted a similar increase in the rate of fractures, from 140,882 in 2012 to 183,105 in 2022.[12]

In addition to significant health and social burden, poor bone health exerts considerable economic pressure on Australia's healthcare system, with the total direct and indirect costs of osteoporosis and osteopenia predicted to reach $3.84 billion by 2022.[12]

Epidemiology

Osteoporosis and osteopenia

Based on the WHO definition of osteoporosis and osteopenia, approximately 3% of men and 13% of women in Australia aged 50–69 years are osteoporotic, rising to 13% and 43% for men and women aged >70 years.[12] Fifty-five per cent of men and 49% of women between 50 and 69 years of age are osteopenic, with a similar prevalence in those aged >70 years.[12] By 2022, approximately 72% of women and 62% of men aged >50 years will have osteoporosis or osteopenia based on WHO criteria.[12,13]

Minimal trauma fractures

Approximately 70% of minimal trauma fractures occur in women, with incidence increasing with age in both sexes.[12] The residual lifetime risk of minimal trauma fracture is approximately 44% for women aged >60 years, which is higher than the risk of ischaemic heart disease or some types of cancers (e.g., breast cancer).[14] In men of the same age group, the lifetime fracture risk is lower (at 25%) and comparable to the lifetime risk of developing diabetes.[14]

Between the ages of 50 and 69 years, non-hip, non-vertebral fractures (humerus, ankle, lower limb, rib, forearm, proximal pelvis, patella, foot, and hand) are the most common minimal trauma fracture types in both men and women.[12,13] Wrist fractures are also common in women in this age group.

Hip fractures

The hip fracture rate increases substantially with age, constituting only 4% of fragility fractures in women aged 50–69 years, but 26% of fractures in women aged >70 years.[12] A similar trend with age is seen in men, although the overall incidence of hip fracture in men remains around one-third that in women.[12] After a rise in the 1980s and stabilisation in the 1990s, the age-standardised hip fracture incidence rate declined in Australia between 1997 and 2007.[15] However, the absolute number of hip fractures increased during this period due to population ageing.[15] Any continued decline in incidence rate will be offset by the ageing population – the number of Australians aged >65 years is set to more than double from 4.2 million in 2020 to almost 10.2 million by 2066.[14]

Vertebral fractures

Vertebral fractures due to osteoporosis are associated with significant long-term disability due to pain and kyphosis. Vertebral fractures are usually defined as a 20% or greater reduction in vertebral height on X-ray and are often termed a 'vertebral deformity'. The prevalence of radiologically identified vertebral deformities ranges from 5% in people aged 50–54 years to 50% in those aged >80 years.[16] In 2012, an estimated 25,502 vertebral fractures occurred in Australia[12] and by 2022 this incidence was expected to rise to over 35,000, an increase of 37%.[12] Underdiagnosis of vertebral fractures is a major problem, because incident radiographic vertebral fractures are associated with a significantly higher risk of subsequent vertebral and non-vertebral fracture.[12] Only around one-third of all radiographically observed vertebral deformities come to medical attention (i.e., are symptomatic with acute fracture-related pain).[17] In Australia, approximately 30% of radiographically visible vertebral fractures in women with osteoporosis are not detected.[18]

Osteoporosis is a systemic condition. Almost all fracture types are increased in patients with low BMD. All fracture sites apart from rib fractures (in men) increase subsequent fracture risk by two- to fourfold.[12,19] Moderate to high trauma fractures are also associated with increased fracture risk.[20]

Morbidity

Fracture-related morbidity can arise from pain, reduced mobility, loss of function and associated reduced quality of life.[21] Many patients lose the ability to live independently following a hip fracture. Long-term morbidity is associated with almost all types of symptomatic osteoporotic fractures; only individuals with wrist, humerus or ankle fractures return to their prefracture health-related quality of life 18 months after fracture.[21]

Mortality

Mortality in the first year after a major minimal trauma fracture in people aged >60 years is up to threefold higher than in age-matched non-fracture populations for people with hip fracture and up to twofold higher for other major fracture types ('major fractures' include pelvis, distal femur, proximal tibia, three or more simultaneous ribs and proximal humerus; 'minor fractures' include all remaining osteoporotic fractures).[3,19,22] The mortality rate (per 100 person-years) is higher in men than in women following any type of minimal trauma fracture; this is most pronounced following hip fracture.[19,22] The risk of death is greatest in the first year after hip fracture: approximately 20% of women die within one year of fracturing a hip, with 10% dying during hospitalisation.[23] Increased mortality during the immediate post-fracture period is associated with advanced age and male sex, and has been linked both to comorbid conditions, such as congestive heart failure and liver disease,[23,24] and to the fracture event itself.[23,24] Acute events, such as postoperative infections and complications, are also important.

Although hip fracture is associated with the highest post-fracture mortality, followed by pelvic and vertebral fractures, one-quarter of excess mortality associated with minimal trauma fracture is attributable to non-hip, non-spine fractures due to the high prevalence of these fractures.[25] Excess mortality occurs mainly in the first five years after a minimal trauma fracture, but may continue up to 10 years following fracture.[26,27]

Osteoporosis treatment has been shown in randomised controlled trials (RCTs) to significantly reduce mortality risk after hip fracture in older men and women,[28,29] and cohort studies suggest this is also the case for other fracture types.[30–32] The mechanisms behind mortality reduction remain speculative but, interestingly, a reduction in pneumonia and cardiovascular events is possible.[33]

Osteoporosis treatment gap in Australia

Any osteoporotic fracture predisposes an individual to at least a twofold increased risk of further fractures,[3,19,34–40] significant morbidity, and premature death.[27,41] In a 2012 report of New South Wales (NSW) hospital admission data from the Agency for Clinical Innovation, 46% of patients with an osteoporotic fracture were readmitted to hospital due to a further fracture.[42]

The timely diagnosis and optimal treatment of osteoporosis prevents further fractures by up to 30%, 50%, and 70% in patients with non-vertebral, hip, and vertebral fractures, respectively.[32,43,44] Safe and effective medications are available for those who have sustained a minimal trauma fracture.[29,45–48] Internationally, however, 70–85% of patients presenting with a minimal trauma fracture to their general practitioner (GP) or hospital are neither assessed for osteoporosis nor appropriately managed to prevent further fractures.[7,9,49–56] Two large retrospective studies of primary care practice in Australia demonstrated that less than one-third of patients presenting with a minimal trauma fracture receive specific anti-osteoporosis pharmacotherapy.[7,56] A recent Australian general practice study further suggests that osteoporosis remains underdiagnosed and undertreated.[9] This treatment gap is also evident in hospitals and tertiary referral centres.[57]

Trends of hip fractures in Australia

The estimated incidence rate of osteoporotic hip fracture in Australia is declining.[58] Over the 10-year period from 1997–98 to 2006–07, the age-standardised rate fell by 14% in men and 20% in women.[58] This reduction mainly occurred among men aged 65–84 years and women aged ≥60 years; little change was seen in those aged 40–59 years. A combination of factors may be responsible for the observed reduction, including measures to reduce risk factors and prevent falls among the ageing.[58–60]

Systematic interventions to address the care gap in osteoporosis management

Fracture liaison services (FLSs) or secondary fracture prevention (SFP) programs are the most proven methods to address the care gap in osteoporosis. These identify patients with a minimal trauma fracture, assess them for osteoporosis, initiate treatment (if appropriate) and communicate with primary care providers. Australian SFP programs have demonstrated improved osteoporosis treatment initiation and reduced refracture rates compared with standard care.[66–68]

The objectives of an SFP program are encapsulated by the '3i's': **identify** patients with osteoporosis; **investigate** and determine fracture and falls risk; and **initiate** interventions to reduce fracture risk. A systematic review divided interventions into four models of care, according to intervention intensity (see **Table 2**).[61] A key aspect of any Type A or Type B SFP program is a coordinator who oversees the program, from initial patient contact following minimal trauma fracture to osteoporosis and falls risk assessment and to follow-up once interventions have been initiated. Once patients are 'captured', most programs perform a full risk factor assessment, including clinical osteoporosis risk factors, falls risk assessment and BMD testing.

Type A (3i) and Type B (2i) SFP programs have been shown in RCTs to improve outcome measures (BMD testing and treatment initiation rates) compared with less-intensive Type C (1i) and Type D (0i) programs,[62,63] while also reducing refracture rates[64–66] in a clinically and economically effective manner.[64,67–70] A 2012 evaluation of the SFP program at Concord Hospital in Sydney, NSW, showed that it was highly cost-effective, with a cost of around $17,000 per quality-adjusted life year (QALY) gained.[68]

A more recent three-year costing study at Newcastle's John Hunter Hospital in NSW also estimated annual savings of between $1.2 million and $1.8 million as a result of investing in its FLS.[71] The burden of refracture on Australia's healthcare system is demonstrated in a recently published 11-year longitudinal analysis of refracture rates in people aged >50 years and public hospital utilisation across NSW, where the annual cost of refracture to NSW Health increased from $130 million in 2009 to $194 million in 2019.[72] If nothing changes, it was estimated this would increase to $2.4 billion over the next decade, providing compelling evidence for implementation of best practice statewide models of care to prevent refractures.[72] However, at the time of writing, NSW remains the only Australian state with a statewide osteoporosis refracture program (ORP) built around FLSs.

Table 2. Description of models of care for secondary fracture prevention according to intervention intensity[62]

Model of care	Description
Type A	Identification, assessment (risk factors, bloods, BMD), treatment initiation and correspondence with GP
Type B	Identification, assessment and treatment recommendation only
Type C	Information given to GP and patient
Type D	Information given to patient only

Role of GPs

FLS and SFP programs run centrally from hospital-based centres have two key limitations:

1. They do not capture all fragility fractures managed by the hospitals in their regions.
2. They lack capacity to manage osteoporosis long-term, as needed.

Furthermore, SFP programs will not capture all patients at high risk of fracture or refracture, such as those with vertebral fracture, frail older people, those in institutionalised care and those with hip fractures managed via orthopaedic pathways.[73]

General practice-led care is critical to manage this common long-term condition. Specialised services should focus on maximising the support and capacity for osteoporosis care in primary care. Almost all patients with a minimal trauma fracture will eventually see their GP (although, not necessarily for a minimal trauma fracture). Orthogeriatric services, which are now present in most Australian hospitals, have also been shown to improve osteoporosis care.[74]

Since the 2013 systematic review of FLS models,[61] FLSs have commenced across NSW with collaboration between hospital and primary care services in many areas. Although not formally evaluated, recent experiences suggest that SFP programs that have a strong relationship with local general practices, including through codesign, may achieve better continuity of osteoporosis care without requirement for the FLS to deliver treatment initiation. HealthPathways is another widely available resource to support GP-led osteoporosis care.

A recent systematic review of orthogeriatric models of care, covering 18 (mainly retrospective cohort) studies from 1992 to 2012, demonstrated a reduction in inpatient mortality (relative risk [RR] 0.60; 95% confidence interval [CI]: 0.43–0.84) and long-term (6–12 months after fracture) mortality (RR 0.83; 95% CI: 0.74–0.94, respectively).[74] Length of stay was reduced in the orthogeriatric care model.[75]

The treatment gap in osteoporosis care in Australia can be addressed through widespread implementation of SFP programs and orthogeriatric services in both hospital and primary care settings. Because general practice is the only extensive workforce capable of long-term care of osteoporosis, supporting GPs to manage osteoporosis is critical to ensuring all patients with a minimal trauma fracture are evaluated and managed appropriately.

Management of osteoporosis in rural and remote areas

In general, there is less utilisation of health services in rural and remote areas, and this is associated with poorer health outcomes.[75] People living in rural and remote areas are more likely to suffer from chronic diseases than those residing in major cities. However, the diagnosis of osteoporosis is more prevalent in major cities than in other areas of Australia.[75]

Women living outside Australia's major cities are slightly more likely to have an osteoporotic hip fracture than those in major cities; rates among men do not vary significantly.[76] Furthermore, those living in remote Australia tend to be younger at the time of first fracture (75 years for men, 79 years for women) than those living in non-remote areas (81 and 83 years for men and women, respectively).[76]

Bone densitometry (DXA) Medicare claims increased by 78% in the 10 years from 2006 to 2015.[76] Despite this, bone densitometry utilisation rates are significantly lower in rural and remote areas than in regional and urban areas, with those residing in capital cities around threefold more likely to undergo bone densitometry than those in remote areas.[75]

There is a particular need to facilitate the detection and management of osteoporosis in rural and remote areas. The fracture liaison coordinator/osteoporosis refracture prevention model of care has been shown to work well in regional NSW.[77,78] Important factors are likely to be limitations in primary healthcare and bone densitometry services in rural and remote areas.

Aboriginal and Torres Strait Islander peoples

The burden of osteoporosis and fracture prevalence in Aboriginal and Torres Strait Islander people is unclear. Aboriginal and Torres Strait Islander adults may be more likely to experience a minimal trauma fracture (men 50% and women 26%) compared with non-Indigenous Australians.[76] Hip fractures appear to occur, on average, at a much younger age in Aboriginal and Torres Strait Islander people than in non-Indigenous Australians (for men, 65 versus 81 years, respectively; for women, 74 versus 83 years, respectively).[79] Over a 10-year period (1999–2009), there was a disproportionate increase in age-related hip fracture rates by 7.2% per year for Aboriginal and Torres Strait Islander people, whereas rates declined by 3.4% per year in non-Indigenous Australians.[80] The prevalence of chronic disease, such as cardiovascular disease, type 2 diabetes and chronic kidney disease, is also higher in Aboriginal and Torres Strait Islander people. These comorbidities are associated with an increased risk of osteoporosis, falls and fracture.[81]

According to self-reported data from the 2018–19 National Aboriginal and Torres Strait Islander Health Survey, the prevalence of osteoporosis among Aboriginal and Torres Strait Islander peoples was 2.3%, affecting 18,900 people, with approximately 1000 living in remote areas (0.7% of the remote Aboriginal and Torres Strait Islander population).[76]

Different patterns of risk factors, such as smoking, poor nutrition, limited exercise, excess weight, and high alcohol consumption, are likely to be important in Aboriginal and Torres Strait Islander peoples. The interaction of these factors on lower life expectancy, higher comorbidity rates, variable access to health services, and socioeconomic factors is difficult to estimate. The promotion of good nutrition and reduction of risk factors is very important for a wide range of health issues, not only osteoporosis. It is expected that Aboriginal and Torres Strait Islander women and men experience at least the same, if not greater, limitation in accessing bone densitometry as other people living in rural and remote Australia.

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Risk factors, fracture risk assessment and case-finding

Identifying patients to investigate for osteoporosis

Identifying patients to investigate for osteoporosis

Recommendations

Recommendation 1	Grade
All individuals over the age of 50 years who sustain a fracture following minimal trauma (such as a fall from standing height, or less) should be considered to have a presumptive diagnosis of osteoporosis.	A
Recommendation 2	**Grade**
Conduct a clinical risk factor assessment in postmenopausal women and men over the age of 50 years with one or more major risk factors for minimal trauma fracture to guide BMD measurement and prompt timely referral and/or drug treatment.[A]	A
Recommendation 3	**Grade**
A presumptive diagnosis of osteoporosis can be made in a patient with a vertebral fracture or hip fracture in whom there is no history of significant trauma. Caution regarding diagnosis and treatment should be exercised if only a single mild vertebral deformity (height loss) is detected, especially in a patient under the age of 60 years.	B

[A] International guidelines recommend fracture risk assessment in post-menopausal women and men aged >50 years.[1-4]

Assessment of clinical risk factors

This section provides an overview of non-modifiable and modifiable clinical risk factors for osteoporosis in postmenopausal women and men aged >50 years. More information and specific references related to these risk factors can be found in other sections as highlighted.

Non-modifiable risk factors

History of minimal trauma fracture

The most easily-recognised risk factor for osteoporotic fracture is the presence of any vertebral or non-vertebral minimal trauma (fall from standing height or less) fracture. This also applies to vertebral fractures incidentally detected on radiographs. A trauma history may guide interpretation of vertebral deformities. Any minimal trauma fracture in someone aged >50 years prompt bone health assessment.[5] DXA may be useful to determine whether the patient has reduced BMD (refer to **Section 1.2**).

Paternal or maternal history of hip fracture

A paternal or maternal history of hip fracture is the most reliable indicator of genetic risk of minimal trauma fracture. However, family history of other types of minimal trauma fracture should also be considered.

Height loss ≥3 cm and/or back pain suggestive of vertebral fracture

Some loss of height is typical with advancing age and is usually due to disc degeneration and/or scoliosis. The accurate measurement and recording of height are important; a height loss ≥3 cm, as measured by stadiometer, requires exclusion of vertebral deformity or fractures by X-ray. The greater the height loss, in the absence of obvious scoliosis, the greater the likelihood of vertebral fractures.

Sex

In each age group, men are at an approximately 50% lower fracture risk than women. However, once a man has experienced a fracture, his risk of a subsequent fracture is equivalent to that of a woman of comparable age who has also experienced a fracture.

Age

Fracture risk is strongly affected by age for both sexes. With each decade of life, the risk of minimal trauma fracture approximately doubles. Age as a fracture risk is independent of both BMD and clinical risk factors, such as risk of falling, which also increase with age and contribute to fracture risk. People aged <50 years are likely to be at low risk of fracture in the absence of other risk factors.

History of falls

A history of falls increases the risk of peripheral minimal trauma fractures for postmenopausal women and men of comparable age. This applies to falls without external cause that have occurred more than once in the past 12 months. Risk factors for falling include poor quadriceps strength, body sway, vitamin D deficiency, medications, visual impairment and environmental hazards (refer to **Section 2.2**).

Premature menopause or hypogonadism

Sex hormone deficiency leads to a reduction in bone mass and increased fracture risk. Early menopause (ie before age 45 years) and male hypogonadism (eg due to androgen deprivation therapy [ADT] to treat prostate cancer) are important causes of secondary osteoporosis. Male hypogonadism results in reductions in bone and muscle mass that improve with testosterone supplementation. Menopausal hormone therapy (MHT) in women with premature menopause mitigates the increase in bone resorption and preserves bone mass (refer to **Section 3.4**).

Modifiable risk factors

Low BMD

Relative fracture risk approximately doubles for each unit (SD) decrease in T-score, as measured by DXA. Postmenopausal women and men aged >50 years with osteoporosis (T-score ≤–2.5) are already at increased risk of minimal trauma fracture. Absolute fracture risk increases with both increasing age and decreasing BMD. The absolute risk for fracture is therefore high in postmenopausal women and men aged ≥70 years with a T-score ≤–2.5 (without fracture) and even higher in those with a T-score ≤–3.0. The strongest association between bone density and fracture risk exists when bone density at one site is used to predict the risk for fracture at that site – hence the focus on BMD at the hip, forearm, and spine[5] (refer to **Section 1.2**).

However, any minimal trauma fracture in someone aged >50 years should be used as an opportunity to assess bone health. Because other factors (e.g., age, falls risk, poor vision) also affect fracture risk, the presence of a normal or only mildly low BMD may mean pharmacological therapy to increase BMD may not be required, and management in that person should focus on fall-prevention strategies.

Low body weight or weight loss

Low body weight (body mass index [BMI] <20 kg/m^2) doubles the relative risk of a hip fracture in both women and men. An increased risk has also been demonstrated for spine and peripheral fractures. Unintentional weight loss is also associated with an increased risk of minimal trauma fracture. Anorexia nervosa is associated with an increased risk of developing osteoporosis.

Low muscle mass and strength

The gradual loss of skeletal mass and strength that occurs with advancing age is associated with an increased risk of falls and fragility fractures. Hip fracture patients with sarcopenia are 1.8-fold more likely to have osteoporosis than hip fracture patients with normal muscle mass.[6] Insufficient protein intake and skeletal muscle inactivity are two important factors that cause skeletal muscle depletion (refer to **Section 1.2**).

Low physical activity or prolonged immobility

A lack of physical activity is a risk factor for hip and vertebral fractures. Limited mobility, so that the person cannot leave home or do housework, may be associated with, and compounded by, low or no exposure to sunlight and subsequent vitamin D deficiency. The inability to rise from a chair without using the arms (a marker of loss of lower extremity strength and power) is associated with an increased risk of minimal trauma fracture (refer to **Section 2.3**).

Poor balance

Poor balance increases the likelihood of a trip, slip, or fall and is a risk factor for hip and vertebral fractures. Balance training in isolation does not improve BMD, although it can reduce falls risk (refer to **Sections 2.2** and **2.3**).

Smoking

For both women and men, smoking is a moderate risk factor for vertebral and non-vertebral (including hip) minimal trauma fractures. Although a dose–response relationship is unclear, smokers generally have a higher fracture risk than non-smokers.

High alcohol intake

Based on general health advice, the National Health and Medical Research Council (NHMRC) currently recommends women and men should drink no more than 10 standard drinks a week and no more than four standard drinks on any one day.[6] In addition to increasing falls risk, high alcohol intake appears to have a deleterious effect on bone-forming cells (osteoblasts), although the specific mechanisms are unclear.[7]

Vitamin D and calcium levels

Suboptimal dietary calcium intake and vitamin D deficiency are important public health problems in Australia. Vitamin D deficiency is associated with a higher risk of falling in older people. Routine screening of serum vitamin D levels should not be conducted. Testing should be restricted to those with suspected or proven osteoporosis, conditions or medications known to decrease vitamin D levels, deeply pigmented skin or severe lack of sun exposure due to cultural, medical, occupational or residential reasons (refer to **Section 2.1**).

Co-existing medical conditions

Co-existing medical conditions include those that increase bone loss or lead to lower BMD at an earlier age, such as rheumatoid arthritis, Type 1 and 2 diabetes, Cushing syndrome (endogenous or exogenous), hyperparathyroidism, hyperthyroidism (or thyroxine excess), chronic kidney disease, chronic liver disease, premature menopause, male hypogonadism, coeliac disease, inflammatory bowel disease or other malabsorption disorders. These conditions are associated with an increase in the age-specific risk for osteoporosis and minimal trauma fractures.

Pharmacological risk factors

Pharmacological risk factors include medications that cause bone loss (e.g., ADT for prostate cancer or aromatase inhibitors for breast cancer; refer to **Section 5.2**).

Medications associated with increased risk of minimal trauma fracture particularly include prolonged glucocorticoids (at least four months cumulative prednisone or equivalent prednisone dose ≥7.5 mg per day). However, other medications associated with increased fracture risk in population-based studies should be considered, such as excessive thyroid hormone replacement[8], selective serotonin reuptake inhibitors[9], proton pump inhibitors[10,11], some antiepileptic drugs[12,13] and certain antipsychotics[14,15]. However, it can be difficult to distinguish medication-related effects on bone health from the effect of the underlying condition that required their use.

Evidence Statement

In patients with a recent minimal trauma fracture, there is a high prevalence of risk factors for osteoporosis that are independent of BMD.[16] This suggests that all postmenopausal women and men aged >50 years should undergo a risk factor assessment for osteoporosis. All patients who sustain a minimal trauma fracture should be screened for risk factors, regardless of BMD, so that action may be taken to reduce the risk of subsequent fractures.

There is strong multinational RCT evidence that mild (Grade 1: 20–25% vertebral height loss) vertebral fractures are a significant risk factor for future vertebral fractures.[17] The risk of new vertebral fracture increases progressively with grade of the initial vertebral fracture; a severe initial fracture is associated with a sixfold increase in the risk of new vertebral fractures in the following three years.[17] A moderate increase in the risk of non-vertebral fractures is also seen following moderate-to-severe vertebral fracture, a finding independent of BMD.[17] The Dubbo Osteoporosis Epidemiology Study found that all fracture types, except ankle and rib fractures, are associated with increased subsequent fracture risk, with even a minor initial fracture resulting in an increased risk of major or hip fracture.[18] Approximately half of refractures occurred in the first two years, and the risk persisted for up to 10 years.[18]

Low BMI is an established risk factor for fracture. A meta-analysis of almost 60,000 participants in 12 prospective population-based cohorts worldwide found that the risk of any type of fracture increased significantly with lower BMI, largely independent of age and sex.[19] Compared with a BMI of 25 kg/m^2, a BMI of 20 kg/m^2 was associated with a twofold increased risk of hip fracture, independent of BMD. The association between high BMI and fracture risk is more complex. A meta-analysis of approximately 400,000 women from 25 prospective cohorts worldwide suggested that, at a population level, high BMI (>35 kg/m^2) was protective for all types of minimal trauma fracture, except for humeral fracture.[20] However, when adjusted for BMD, obesity slightly increased the risk of all fractures. Weight fluctuation also appeared to influence fracture risk. Post hoc analysis of data from over 120,000 women taking part in the Women's Health Initiative (WHI) observational study and clinical trials demonstrated that both weight gain and weight loss are associated with increased fracture incidence.[21] Women who lost more than 5% of baseline body weight over three years had a 65% increased risk of hip fracture than those who maintained stable weight for three years. Significantly, higher rates of spinal fracture were also seen in the former group. A 5% weight gain over three years was associated with a higher incidence of upper and lower limb fractures.[21] The relationship between body weight and fracture risk is complex.

Smoking is a well-recognised risk factor for osteoporosis. A meta-analysis of over 59,000 men and women in 10 prospective cohort studies found that current smoking was significantly associated with an increased risk of any fracture compared with non-

smokers (RR 1.25; 95% CI: 1.15–1.36). The highest risk was seen for hip fracture.[21] A past history of smoking was also associated with significantly increased fracture risk in that analysis. The risk was lower than for current smoking, indicating that risk was attenuated with smoking cessation. Although smokers tended to be thinner than non-smokers, low BMD could only account for 23% of smoking-related hip fractures in this study, indicating a potential direct effect of cigarette smoke toxins on bone metabolism.[22]

Excessive alcohol intake is also associated with increased fracture risk. A systematic review and meta-analysis of 22 observational studies suggested a significantly increased risk of fracture in men consuming alcohol daily or consuming more than 10 drinks per week (RR 1.28; 95% CI: 1.08–1.53).[23] An analysis of three prospective cohorts (approximately 6000 men and 11,000 women) also found a significant increase in hip fracture risk with alcohol intake, although no increased risk was seen in men and women consuming two units or less of alcohol daily.[24] Risk was only marginally lower in women than in men.[24] These observations were independent of BMD.[24] GPs should consult RACGP guidelines that outline preventive health strategies and smoking-cessation interventions.[25–27]

Practical tips and precautions

- Any postmenopausal woman or man aged >50 years that sustains a fracture after minimal trauma (fall from standing height or less) should be considered as having osteoporosis.
- Bone densitometry can exclude pathological causes of fracture, although it is not always required following hip or vertebral fracture.
- BMD is helpful for risk stratification and provides a baseline from which to assess pharmacotherapy response.
- Patients should be assessed for possible vertebral crush fractures if there is well-documented height loss of ≥3 cm (measured by stadiometer), kyphosis, or unexplained back pain. A lateral thoracolumbar X-ray should be performed. If vertebral crush fractures are detected, bone densitometry (DXA) is recommended to determine BMD at the hip and spine.

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Measurement of Bone Mineral Density

Measurement of BMD

Recommendations

Recommendation 4	Grade
Measure BMD by DXA scanning on at least two skeletal sites, including the lumbar spine and hip, unless these sites are unsuitable (eg hip prosthesis).	A

The WHO international reference standard for osteoporosis diagnosis is a T-score of −2.5 or less at the femoral neck (FN).[1] The reference standard from which the T-score is calculated is the female, White, age 20–29 years, Third National Health and Nutrition Examination Survey (NHANES III) database, or equivalent. Osteoporosis may be diagnosed in postmenopausal women and men aged >50 years if the T-score of the lumbar spine, total hip or FN is −2.5 or less. In certain circumstances, the 33% radius (also called the 'one-third radius'; i.e., distal forearm) may be used.[2] The WHO BMD diagnostic osteopenia and osteoporosis classifications should not be used in premenopausal women and in men <50 years of age, or in children. In these patient groups, the diagnosis of osteoporosis should not be made using DXA criteria alone.[2]

As a reference for fracture risk calculation in women in Australia, T-scores calculated from the Geelong Osteoporosis Study database are used for the lumbar spine and proximal femur. Normative data in Australian men are not currently available. Most BMD assessments currently report hip T-scores for men based on the US NHANES III normative data. There are no standardised reference ranges for spine BMD in men and the only option is the use of reference ranges provided by densitometer manufacturers. In some cases, this may change the diagnostic classification.[3]

Dual energy X-ray absorptiometry

DXA is the current gold standard for the diagnosis of osteoporosis. The best sites at which to measure BMD for prediction of future fracture risk are the lumbar spine and the proximal femur.[2,4] Both sites should be measured with consideration to dual hip scanning. DXA is reliable, with a reported precision

of approximately 1%, although in routine clinical practice this is closer to 2%.[2] At this level of precision, the least significant change at the lumbar spine would be 5.6% between measurements, with 95% confidence that the change is real.

Each SD reduction in FN BMD increases the age-adjusted risk of hip fracture by a factor of approximately 2.5 (range 2.0–3.5), whereas the risk attributable to any minimal trauma fracture is almost the same (range 1.7–2.4). Similarly, each SD reduction in lumbar spine BMD increases the risk of spinal fracture by a factor of approximately 2.3 (range 1.9–2.8). FN and total hip BMD appear the best overall predictors of fracture risk. Total hip is the better site for monitoring BMD because it has good precision (less affected by positioning) and is relatively unaffected by osteoarthritis, which can spuriously elevate spinal BMD values, as can vertebral fractures and arterial calcification.[2,5]

Initial assessment of BMD

The initial assessment of BMD by DXA has the following aims:

- to determine the patient's BMD: Fracture risk is multifactorial and may be significantly elevated in individuals outside the osteoporotic range. However, the use of the osteoporotic T-score threshold is the criterion by which healthcare funders define osteoporosis, as well as being consistent with studies in which antifracture effects of anti-osteoporotic drugs have been demonstrated.
- to determine the precise extent of BMD reduction: This is important for refining assessment of individual fracture risk and the extent of recommended therapeutic measures. Absolute fracture risk algorithms (e.g., FRAX® [available at https://fraxplus.org (https://fraxplus.org)] or the Garvan Fracture Risk Calculator [available at www.garvan.org.au/bone-fracture-risk (http://www.garvan.org.au/bone-fracture-risk)]) may be useful in more accurately determining individual fracture risk and assisting the patient in making a treatment decision (refer to **Section 1.3**).

Repeat BMD testing

Repeat DXA scans at intervals of two years or longer can be considered to assist risk assessment or when a change or interruption in treatment is being considered (also refer to **Section 4**).[6–8] The treatment-related change in BMD correlates with the proportion of fracture risk reduction.[7–9] In addition, repeat BMD measurement can identify people with ongoing bone loss, which is an independent predictor of fracture risk.[6] Repeat DXA scans may improve adherence to therapy in some people.[10] However, a minimum of two years may be needed to reliably measure a change in BMD due to limitations in DXA precision. If BMD is stable and/or the individual is at low risk of fracture (normal or mild osteopenia; T-score >−1.5), less frequent monitoring, up to an interval of 5–15 years, can be considered. Shorter intervals between repeat DXA scans at intervals of one year may be appropriate in high-risk individuals (e.g., patients on corticosteroid therapy or ADT for prostate cancer). In all cases, the expected rate of change in BMD and fracture risk should guide repeat measurement.[6]

Quantitative computed tomography assessment of BMD

Quantitative computed tomography (QCT) BMD measurement can provide equivalent hip BMD to DXA scans and may be interpreted using the WHO T-score criteria.[1] Spinal QCT also provides information on fracture risk, but it is important to note the WHO T-score osteoporotic criteria cannot be applied in this situation.[11]

Fracture risk using QCT of the spine is mostly interpreted using American College of Radiology criteria.[12] There are no data demonstrating a reduction in fracture risk by specific anti-osteoporotic treatment chosen based on QCT measurements. However, given the equivalency of hip QCT to hip DXA, there is no reason to doubt the utility of hip QCT in guiding therapy.[13] The disadvantage of QCT remains the significantly higher radiation exposure compared with DXA,[13] particularly at the hip. DXA of the spine and hip remains the recommended measurement for the diagnosis of osteoporosis and baseline BMD assessment. In some patients with moderate-to-severe osteoarthritic changes, spine QCT may have a particular advantage because it is less affected by osteoarthritic changes than DXA.

Other diagnostic investigations

Quantitative ultrasound

Quantitative ultrasound of the heel and other sites can provide information on fracture risk.[2] However, quantitative ultrasound has not been demonstrated to provide information on absolute fracture risk and reduction of fracture risk by anti-osteoporotic treatment. DXA measurements at the spine and proximal femur are preferred for making therapeutic decisions and should be used, if possible. Quantitative ultrasound is not recommended as a routine diagnostic test for osteoporosis.

Biochemical markers of bone turnover

Increased biochemical markers of bone turnover in the blood and/or urine (e.g., serum C-terminal telopeptide or serum alkaline phosphatase) have been shown in trials to be independent risk factors for fractures in women and men.[14] Bone turnover markers are useful markers of medication adherence and response to treatment, and may help guide choice of treatment. Short-term treatment-related changes in bone turnover markers account for a large proportion of the treatment effect of vertebral fracture.[15] However, variability in analysis and lack of standardisation may reduce the utility of these assessments on an individual basis in routine clinical practice.

Practical tips and precautions

- For patients with ready access to DXA, a BMD measurement before commencing therapy is recommended. A normal or near-normal BMD despite existing fractures should prompt a more extensive work-up to exclude other causes of fracture.
- A normal BMD despite typical vertebral fractures also poses a problem regarding the usefulness of anti-osteoporotic treatments that have not been tested in such a population.

Such discrepant findings should be resolved on an individual basis and may require specialist (e.g., endocrinologist, rheumatologist) referral.

- A history of high-trauma falls resulting in vertebral fracture can leave evidence of vertebral deformities that may not indicate underlying osteoporosis. In such situations, consultation with a specialist may be warranted.
- Conventional radiographs should not be used for the diagnosis or exclusion of osteoporosis.
- Evaluation of osteoporosis is based on the lower T-score of either the lumbar spine, FN or total hip.[1]
- The BMD at the forearm may be measured by DXA, but caution is advised because there are limited data on its use in guiding therapy.
- Repeat BMD measurements may be performed to assess the efficacy of treatment and residual fracture risk or to assist in improving patient medication adherence.
- If possible, it is recommended repeat BMD tests are performed using the same instrument or at least the same make of instrument (manufacturer and model type) to improve the comparability of results in interpreting BMD change.[6]
- Relevant blood and urine studies should be obtained prior to initiating therapy if the medical history and/or clinical examination is suggestive of secondary osteoporosis, or the DXA Z-score is ≤−2.0 (i.e., two or more SDs different from age- and sex-matched controls).[16]
- If radiographs reveal one or more vertebral fractures typical of osteoporosis, BMD measurement may not be essential before starting medical therapy, if clinically appropriate. There are a limited number of scenarios in which meaningful evaluation of BMD is not possible (e.g., bilateral hip replacements and osteoporotic fractures in the lumbar spine region of BMD measurement [L2–4]). In such cases, it should be assumed that BMD measurement would have been low and that therapy is likely to be beneficial. Forearm BMD may be useful; however, its precise value has not been as well characterised as spine and hip BMD.

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Assessment of absolute fracture risk

Assessment of absolute fracture risk

Recommendations

Recommendation 5	Grade
Assessment of absolute fracture risk, using the Fracture Risk Assessment Tool (FRAX®; https://fraxplus.org (https://fraxplus.org)) may be useful in assessing the need for treatment in individuals who do not clearly fit established criteria.	B
Recommendation 6	**Grade**
Patients with a very high and/or imminent fracture risk should be promptly referred to a specialist for consideration of osteoanabolic therapy as first-line treatment.	C

In addition to BMD, there are other clinical factors associated with minimal trauma fracture risk. Two individuals with similar BMD measurements but different clinical risk factors will have different fracture risk. Increasing age, prior minimal trauma fracture, and propensity to fall are the clinical risk factors most strongly associated with increased fracture risk.[1] Fracture risk may be expressed as either relative or absolute risk.

Absolute risk is the numerical risk of an event for an individual over a specified period. This is commonly expressed as an individual's percentage chance of suffering a minimal trauma fracture over a given period, generally five or 10 years. Relative risk compares an individual's risk of an event (such as a fracture) to the risk of that event in a reference population, or to the baseline risk at a given time point. An individual's relative risk will depend on the comparison group used. Assessing only relative risk can

lead to erroneous conclusions. For example, if the background absolute risk of a fracture at a given time is low (e.g., 0.2% five-year risk), then even with a doubling of risk (relative risk increases to 2), absolute risk remains low (0.4% five-year risk).

Imminent and very high/high fracture risk

Imminent fracture risk

The identification of patients at imminent or very high/high fracture risk is emerging as an important part of osteoporosis care. Imminent fracture risk could either be interpreted as the short-term (1–2 year) absolute fracture risk or the markedly high fracture risk period following the incident fracture (e.g., patients with a fracture within the past 24 months).

Very high and high fracture risk

In addition to a BMD T-score ≤−3.0, the following risk factors may further increase fracture risk: concurrent glucocorticoid therapy; low BMI; and recent acute weight loss and recurrent falls. 'Very high fracture risk' is an evolving concept with variability in definition. For example, the US Endocrine Society defines 'very high risk' as an individual with multiple spine fractures and a T-score of ≤−2.5.[2] The Scottish Intercollegiate Guidelines Network uses a similar approach, defining severe osteoporosis as the presence of one severe or two or more moderate vertebral fractures with a T-score of ≤−1.5, or a lumbar spine T-score of ≤−4.0, regardless of fracture.[3]

Recent UK guidelines suggest that 'very high fracture risk', incorporating the concept of imminent fracture risk in the shorter term, may be captured by the presence of a recent fracture and a 10-year FRAX® major osteoporotic fracture risk of ≥30%.[4] The American Association of Clinical Endocrinologists also defines 'very high fracture risk' as including a recent fracture (within 12 months), a T-score of <−3.0, multiple fractures while on therapy, the use of drugs causing skeletal harm, and a 10-year FRAX® major osteoporotic fracture risk of ≥30% or hip fracture risk of >4.5%.[5] Not all criteria need to be present in the one patient, and instead, they are meant to represent different patient groups at very high fracture risk.[5] Across guidelines, the most common criteria were a recent fracture (within 12 or 24 months), multiple fractures, fractures while on therapy, and a 10-year FRAX® major osteoporotic fracture risk of ≥30% or a hip fracture risk of >4.5%.[3–5] Although more data are required to cement an internationally accepted definition, these various definitions highlight the types of patient who should be identified for prompt specialist referral, especially if the fracture has occurred within two years with multiple clinical risk factors (e.g., glucocorticoid use, falls, rheumatoid arthritis, and age ≥70 years).[6,7]

Although advanced age is associated with a greater risk of osteoporotic fracture, younger patients may also be at very high fracture risk, and early identification and specialist referral of these patients is warranted. Exclusion of secondary causes of osteoporosis and consideration of osteoanabolic therapies (i.e., drugs that form new bone; refer to **Sections 3.3** and **3.5**) should be undertaken. In the absence of access to specialist care, early initiation of parenteral antiresorptive therapy should be considered with regular review.

Absolute fracture risk calculators

Several absolute fracture risk calculators are available. These aim to better estimate an individual's fracture risk by considering age and clinical risk factors, as well as BMD, and may allow more effective targeting of therapy for osteoporosis. The Garvan Fracture Risk Calculator (https://www.garvan.org.au/promotions/bone-fracture-risk/calculator/ (https://www.garvan.org.au/promotions/bone-fracture-risk/calculator/)) was developed in Australia using data from the Dubbo Osteoporosis Epidemiology Study.[8] FRAX® (https://fraxplus.org (https://fraxplus.org)) uses data from nine epidemiological studies, including the Dubbo Osteoporosis Epidemiology Study, as well as results from the placebo arms of clinical trials to estimate absolute fracture risk.[9]

DXA scanners that incorporate specialised software can provide a FRAX® estimate of absolute fracture risk. The three international studies of a population-based fracture screening program have used FRAX®.[10–12] FRAX® models are currently available in 73 countries covering around 80% of the world population, and the tool is used in over 100 guidelines worldwide.[13–15]

While aiming to achieve the same outputs, FRAX® and the Garvan Fracture Risk Calculator use different algorithms and inputs to estimate absolute fracture risk (refer to **Table 3**). Both have similar predictive discriminative ability (area under the curve range 0.67–0.70 for hip fracture, 0.62–0.64 for osteoporotic fracture and 0.60–0.63 for any fracture).[16] The input factors for FRAX® are listed in **Table 3**. FN BMD is an optional input.

Table 3: FRAX® and Garvan Fracture Risk Calculator input factors

	FRAX®	**Garvan Fracture Risk Calculator**
Age	Graded	Graded
Sex	Binary, (ie yes/no)	Binary
Ethnicity/nationality	Graded	Not Included
BMI	Graded	Not Included
BMD	Graded	Graded
Prior fracture	Binary	Graded
Falls	Not Included	Graded

Glucocorticoid use	Binary	Not Included
Family history of fracture	Binary	Not Included
Rheumatoid arthritis	Binary	Not Included
Smoking	Binary	Not Included
Alcohol use	Binary	Not Included
Secondary osteoporosis	Binary	Not Included

The limitations of FRAX® have been extensively discussed.[17,18] In particular, secondary causes of osteoporosis are assigned an identical risk using binary (yes/no) responses only, falls are not considered, and the calculation algorithm is not publicly available.[19]

However, most international guidelines suggest its use[3–5,13] due to the wide validation of FRAX® in multiple large international populations, ease of access as part of DXA machine software, and ongoing refinement with responsiveness to user feedback.[20] A unique feature of FRAX® is its consideration of the competing hazard of death, meaning that fracture risk is reduced in those with low life expectancy (e.g., older, frailer people). For these reasons, FRAX® appears the most robust fracture risk calculator, especially as ongoing refinements to it are being implemented. Clearly, clinical judgement is still required to interpret FRAX® outputs of 10-year fracture risk.

However, the Garvan Fracture Risk Calculator still has a role. Its simplicity, requiring only five input factors, makes it very convenient. Exclusion of falls as a risk factor by FRAX® leads to a marked divergence in risk estimates between it and the Garvan Fracture Risk Calculator for patients with frequent falls.[21] Hence, using the Garvan Fracture Risk Calculator in patients with falls may be more appropriate.

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Case-finding and screening

Case-finding and screening

Recommendations

Recommendation 7	Grade
Those aged >50 years with a current or prior minimal trauma fracture should be assessed and appropriately treated.	A
Recommendation 8	**Grade**
For those aged >50 years with lifestyle and non-modifiable risk factors (eg parent with hip fracture) use FRAX® to calculate absolute fracture risk. When FRAX® risk for major osteoporotic fracture (MOF) is ≥10%, refer for DXA. If the risk of MOF is <10%, DXA is not recommended. Re-stratify risk with FRAX® after DXA using BMD reading and treat when: • BMD T-score is ≤−2.5 • BMD T-score is between −1.5 and −2.5 and the FRAX® risk for MOF is ≥20% and/or the hip fracture risk is ≥3%.	D
Recommendation 9	**Grade**
For those aged >50 years with diseases/chronic conditions/medications associated with increased fracture risk, refer for BMD assessment by DXA. Re-stratify risk with FRAX® after DXA using BMD reading and treat when: • BMD T-score is ≤−2.5 • BMD T-score is between −1.5 and −2.5 and the FRAX® risk for MOF is ≥20% and/or the hip fracture risk is ≥3%.	C

Recommendation 10	Grade
There is insufficient evidence to recommend population-based systematic screening with BMD measurement for reduction of osteoporotic fractures in Australia, and case finding is recommended.	B

Screening is the application of a test or assessment to asymptomatic people in defined parts of the population. This can be organised proactively, as seen for bowel or breast cancer, or opportunistically when a person interacts with a health service for other reasons. The case for screening in osteoporosis is for primary prevention of fractures. Case finding is aimed at individuals who would likely accept and benefit from further assessment or investigation. Patients with a previous osteoporotic fracture should be considered for treatment, not screening. As discussed in the Background section, large numbers of people suitable for secondary fracture prevention treatment are being missed, and systems such as osteoporosis refracture prevention programs to identify them are recommended. Active case finding for prior fragility fracture should be considered by radiology services, hospitals and general practitioners.

Currently, there is no universally accepted policy for population-based screening to identify people likely to benefit from osteoporosis treatment.[1] There have been three recent large population-based RCTs of screening in women for the prevention of osteoporotic fractures: Screening in the Community to Reduce Fractures in Older Women (SCOOP) in the UK,[2] Risk-stratified Osteoporosis Strategy Evaluation (ROSE) in Denmark,[3] and SALT Osteoporosis Study (SOS) in the Netherlands.[4] None of these RCTs showed a reduction in their primary outcome of all fractures; however, there was a trend to a reduction. The planned secondary end point of a reduction in hip fractures showed a significant result in one trial and a consistent trend in the other two.[2–4] This resulted in a significant result for hip fracture reduction in a meta-analysis (which included n>42,000 in total), with an absolute risk reduction of 0.47% over five years of treatment.[5] Although this is promising, optimal thresholds of absolute fracture risk and implementation strategies are inadequately defined for the Australian context and there are no data on screening for men. Accordingly, there is currently insufficient evidence to support a population-based screening program in Australia.

Consequently, a case finding strategy is appropriate where patients are identified because of the presence of other clinical risk factors and if they are interested to know their fracture risk to make an informed decision regarding treatment/management, as appropriate.

Fracture-risk intervention threshold

An important application for fracture risk calculators is to improve the selection of individuals in whom to recommend treatment. Individuals who have not fractured but are in the osteoporotic BMD range or middle-aged to older individuals with prior minimal trauma fracture generally have high calculated absolute fracture risk, supporting a recommendation for treatment. Individuals with BMD values within

the osteopenic range but without a prior fracture are more likely to benefit from fracture risk algorithms. In this group, a high fracture risk estimate may change management and lead to therapy recommendation. Health economic modelling in the UK[6,7] and the US[8] has demonstrated that treatment is cost-effective when FRAX® is used to identify at-risk patients. Based on a drug cost of US$600 per year for five years (with 35% fracture reduction) and an average cost per QALY designated at US$60,000 or less, the US National Osteoporosis Foundation guidelines recommend treatment when the 10-year risk of hip fracture estimated by FRAX® is ≥3% or the 10-year risk of major osteoporotic fracture is ≥20%.[9]

A rational approach to assessment and BMD testing

One of the challenges in managing patients suspected of having osteoporosis and at increased risk of fracture is understanding how fracture risk assessment tools, bone densitometry, and the use of anti-osteoporosis therapies can fit together to benefit patients.

A check for the presence of risk factors is reasonable from the age of 50 years onwards because the prevalence of risk factors increases from this age upwards. Risk factors and the influence of sex can be incorporated into a better understanding of an individual's risk through use of an absolute risk calculator. There are many clinical risk factors for fracture in addition to those included in FRAX® that can be used to trigger fracture risk assessment (e.g., inflammatory arthritis or coeliac disease). Several diseases (e.g., rheumatoid arthritis, thyroid disease) and medications (e.g., corticosteroids) on their own are also regarded as sufficient risks for osteoporosis to warrant BMD measurement. This implies the use of FRAX®-based risk estimation prior to BMD is most relevant to those weaker clinical risk factors and age (refer to the 'Osteoporosis risk assessment, diagnosis and management flow chart (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/osteoporosis/osteoporosis-risk-assess-diagnosis-and-management) '). Clinical judgment is needed when clinical risks exceed those that can be incorporated into a FRAX® assessment. This approach of recommending a BMD on the basis of FRAX® risk has been adopted in several countries.[1] The use of a risk estimation tool such as FRAX® also removes the need to set different minimum ages for initial risk enquiry for men and women because sex is part of the risk estimation algorithm.

The absolute risk at which to recommend DXA and the threshold for treatment, especially pharmacotherapy, is important, yet not consistently defined. The level of risk perceived as 'high' will vary between individuals and may differ from the point of view of a funder. Bone density alone is not sensitive for predicting fragility fractures given that most fragility fractures occur in people in the osteopenic range. This can be improved by the use of absolute risk estimation tools, but at the expense of added complexity for the clinician. However, almost all anti-osteoporosis treatments have been studied in RCTs of patients with low BMD values and/or prior fracture rather than based on absolute risk estimation. Three trials allow an estimate of absolute risk at which treatment is effective, as detailed below.

In the Fracture Intervention Trial (FIT) trial (oral alendronate), which was effective at reducing fractures, 90% had a baseline 10-year fracture risk >14%, with virtually all having a risk >10%.[10] In the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every Six Months (FREEDOM) trial, the median baseline 10-year fracture risk was 15%.[11] Denosumab seemed effective for those with a baseline

10-year fracture risk >12%.[11] In the third trial, which evaluated zoledronate in osteoporotic women aged >65 years, zoledronate was effective, with a median baseline absolute risk of 12% for fracture at 10 years.[12]

The thresholds used in the screening trials can also inform the decision to refer for DXA. The ROSE study used a threshold of 15% 10-year fracture risk (FRAX®) to recommend DXA testing.[3] The SCOOP trial used a range of age-specific thresholds (3.4% at 50 years, rising to 11.1% 10-year risk of major osteoporotic fracture at 70 years),[2] which may make implementation in the Australian primary care setting difficult without clinical decision support software or a graphic reference of risk thresholds by age.

Given that case finding would be used for a population selected for their interest to engage in fracture prevention interventions, the impact can be expected to be better than demonstrated in the population screening trials. A slightly lower threshold for recommending BMD assessment has been adopted, as was done in the Scottish Intercollegiate Guidelines Network 2021,[13] where a 10-year risk of major fracture of >10% triggers a recommendation for BMD measurement, which is relatively pragmatic and inclusive. A patient's personal meaning and value placed on a risk estimate should also guide the next steps.

Economic modelling of potential population screening regimens suggests a higher risk threshold is needed to be cost-effective. The absolute risk thresholds for cost-effectiveness were similar across ethnic and racial groups, and slightly higher for men. This assumes five years of full medication adherence. A 2013 Japanese study suggested screening women with a 10-year risk of osteoporotic fracture >26% would be cost-effective at US$50,000/QALY.[14]

Evidence statement for population screening

The SCOOP RCT recruited woman aged 70–85 years from primary care practices in the UK and showed that a screening program using FRAX® first, followed by DXA in those at high risk of hip fracture (probability 5.2–8.5%, depending on age), was associated with a reduction in hip fracture incidence (hazard ratio [HR] 0.72; 95% CI: 0.59–0.89) compared with those undergoing usual care.[2] However, there was no reduction in the prespecified primary outcome of all osteoporosis-related fractures. The use of bone-protective therapy was also higher in the screened group and, in subsequent analysis, medication adherence was increased, even out to 60 months.[5] Of note, fracture probability was then recalculated using the BMD result, and those with a fracture risk above the intervention threshold (hip fracture probability between 5.24% and 8.99%, depending on age) were advised to make an appointment with their GP to discuss potential treatment.[2] The GP was also informed about the screening result.

The Danish community-based ROSE study enrolled woman aged 65–80 years and used data obtained from a self-administered questionnaire to calculate an absolute risk of fracture using FRAX®, followed by a DXA scan in women with moderate-to-high fracture risk (≥15% at 10 years).[3] Unlike the SCOOP trial, there was no difference in fracture incidence between the screening and control groups in the intention-to-treat analysis, possibly because treatment decisions were based on DXA results only.[3] However, another randomised large community-based Dutch study of women aged 65–90 years examined the effect of a screening program involving DXA, vertebral fracture assessment and FRAX®, and failed to show a reduction in fractures compared with usual GP care.[4] However, this may have been affected by suboptimal patient participation and incomplete medication adherence.

Due to concern that the above individual studies may have been underpowered, a subsequent meta-analysis was undertaken and found a statistically significant reduction in osteoporotic fractures (HR 0.95; 95% CI: 0.89–1.00), major osteoporotic fractures (HR 0.91; 95% CI: 0.84–0.98) and hip fractures (HR 0.80; 95% CI: 0.71–0.91), but no reduction in all fractures (HR 0.95; 95% CI: 0.89–1.02).[5] The pooled HR for the secondary outcome of all-cause mortality was not significant at 1.04 (95% CI: 0.95–1.14). The number needed to screen to prevent one fracture was 247 for osteoporotic fractures and 272 for hip fractures.[5] This suggested that population screening might be effective in reducing osteoporotic fractures and hip fractures. Of the three recent RCTs using FRAX®,[2–4] only the SCOOP study has published a cost-effectiveness analysis, which found that a widespread community-based screening program of fracture risk in older UK woman was likely to be cost-effective.[15] Widespread applicability to the Australian population remains to be determined, mainly due to the lack of an Australian-specific treatment threshold

above which bone-protective pharmacotherapy should be commenced. However, a population fracture risk screening program based around the FRAX® tool and DXA appears promising.[16]

Key messages

1. An initial FRAX® assessment, which provides the 10-year probability of MOF (clinical spine, hip, forearm or humerus) and/or hip fracture, can be used to risk stratify patients.
2. Consider, particularly in older people, drug treatment in those with a prior and/or recent fragility fracture, with fracture risk assessment informing the choice of drug treatment, particularly the need for bone anabolic therapy.
3. When BMD is included in a FRAX® assessment, the patient's risk (high, very high or low) is determined by the higher of the two (MOF and hip fracture) risk assessments. (Note: 'High' is MOF risk ≥20% and hip risk ≥3%; 'very high' is MOF risk ≥30% and hip risk ≥4.5%.[17])
4. Men and women with low fracture risk and without a prior fragility fracture can be reassured their fracture risk is low and offered lifestyle advice, as appropriate.
5. Consider referral of patients at very high risk to an endocrinologist or rheumatologist for assessment and consideration of parenteral treatment or first-line osteoanabolic drug treatment, especially those with multiple vertebral fractures. Indications for specialist referral may include a BMD T-score ≤–3.0 and one or more of the following:
    - treatment with glucocorticoids (refer promptly given rapid bone loss after initiation of glucocorticoids; if any delay is anticipated, start an oral bisphosphonate in the meantime)
    - the presence of multiple clinical risk factors, particularly with a recent fragility fracture indicating high imminent risk of refracture
    - other indicators of very high fracture risk (see **Section 1.3**).

Practical tips and precautions

- Absolute fracture risk is not a qualifier for access to PBS-subsided therapy.
- Estimation of absolute fracture risk using a fracture risk calculator does not consider lumbar spine BMD, and such estimates should not disqualify therapeutic decisions based on a low lumbar spine T-score.
- Calculator-based estimations of fracture risk are estimates only, and should always be interpreted in the clinical, racial, and cultural context of the patient.
- Strong shared decision making is important for treatment adherence given bone-protective treatment is long term and for risk management rather than symptom relief. Fracture risk assessment tools may be most useful for this reason.
- When using the FRAX® tool (https://fraxplus.org (https://fraxplus.org)), ensure to select 'Calculation tool' → 'Oceania' → 'Australia'.

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General bone health maintenance and fracture prevention

General bone health maintenance and fracture prevention

Fracture risk increases over the lifetime due to declining BMD and strength, as well as non-skeletal risk factors for falls, including sarcopenia, poor balance, neuropsychological impairment, polypharmacy, poor nutrition and chronic diseases. As such, there is a gradual transition from prevention to treatment paradigms with advancing age, with the emphasis on optimisation/preservation of BMD from childhood to middle age broadening to other factors implicated in falls risk in later life.

Osteoporosis is associated with several lifestyle factors, including nutritional intake, vitamin D status and physical activity. International guidelines recommend healthy lifestyle choices to reduce osteoporosis risk.[1,2]

Calcium, protein and Vitamin D

Calcium, protein and Vitamin D

Recommendations

Recommendation 11	Grade
For generally healthy older people: Although the absolute benefit of calcium and vitamin D supplements in short-term (less than six years) studies for fracture reduction is low, there is good evidence adequate calcium intakes and vitamin D status are important for long-term maintenance of bone and muscle function.	C
Recommendation 12	**Grade**
For frail and institutionalised older people: Calcium and vitamin D supplementation, together with adequate protein intake, are recommended for fracture prevention. Optimisation of calcium and vitamin D should be the standard of care for this group.	B
Recommendation 13	**Grade**
For people taking osteoporosis treatments: • Calcium supplements should be recommended if their dietary calcium intake is less than 1300 mg per day. • Vitamin D supplements should be recommended to correct low serum vitamin D levels (25-hydroxyvitamin D <50 nmol/L).	C
Recommendation 14	**Grade**

For most people with olive or pale brown skin, no other risk factors and who are at intermediate risk of skin cancer, a few minutes of sunlight exposure towards the middle of the day, with time depending on latitude, season and skin area exposed, followed by further sun protection measures should maintain vitamin D levels. People with dark skin at low risk of skin cancer have less need for sun protection, but require more time outdoors to avoid vitamin D deficiency. People at high risk of skin cancer need sun protection most of the year, which may limit vitamin D synthesis. The use of sunscreen, in practice, does not greatly affect vitamin D status.	B

Calcium

Calcium is an important component of bone, accounting for 30–35% of its mass and much of its strength. Bone calcium also acts as a reservoir for maintaining blood calcium levels, which are needed for healthy nerve and muscle function.

Evidence for the relationship between dietary calcium intake and fracture risk reduction has been contradictory due to different methods of assessing calcium intake and the problems inherent in self-reporting of calcium intake, together with genetic, environmental, and sociological differences.

Advice on calcium consumption varies internationally. In Australia, the NHMRC recommended dietary intake (RDI) is 1300 mg per day for women aged >50 years, 1000 mg per day for men aged 50–70 years, and 1300 mg per day for men aged >70 years,[3] similar to the recommendations of the Institute of Medicine in the US,[8] although substantially higher than those of the National Institute for Health and Care Excellence (NICE) in the UK. Increasing calcium intake from food is recommended because, with ageing, enteric calcium absorption becomes less effective and urinary calcium loss increases.[4–6] The importance of adequate calcium intake throughout life for building and maintenance of the skeleton is supported by previous Australian and New Zealand guidelines[7] and those of other countries.[8] Only 20–40% of the Australian adult population meet the calcium RDI. In 2011–12, the average daily intake for people aged 51–70 years was 781 mg for men and 741 mg for women, with intakes lower in people aged >70 years.[9]

Calcium is available from many foods. This provides consumers with a range of calcium sources to meet individual preferences and/or dietary requirements, including those with diverse cultural eating patterns. It is important to note that the calcium content in different foods varies and to focus on the foods that provide the highest content to meet RDIs. The richest sources of dietary calcium are dairy foods – milk, hard cheese, and yoghurt – and, according to current NHMRC Australian dietary guidelines, at least three serves of dairy food per day are recommended (where one serving = 250 mL milk, 200 g yoghurt or 40 g cheese).[3] This adds to the approximately 300 mg of calcium in a non-calcium-rich diet. Other calcium-rich foods include firm tofu, almonds, sesame seeds, tinned fish, some green leafy vegetables, dried figs, and calcium-fortified non-diary milks.[10]

Protein

Protein is an important constituent of bone and muscle tissue. It provides the structural matrix of bone where calcium is the key mineral and collagen (and other non-collagenous proteins) form the organic matrix of bone. Adequate intake of dietary protein is important for bone acquisition and maintenance, as well as for maintenance of the musculoskeletal system.

Protein intake may play a beneficial role in the prevention of bone loss and in slowing down osteoporosis, and has recently gained much attention. A 2018 expert consensus paper summarising systematic reviews and meta-analyses investigating the effects of dietary protein on bone health in adults concluded that an intake above current RDI (0.8 g/kg body weight per day), in combination with an adequate calcium intake, is associated with higher BMD, lower rate of bone loss, and modestly reduced fracture risk.[11] Updated systematic reviews and meta-analyses focusing specifically on adults aged ≥65 years showed a positive trend between higher protein intake and higher femoral neck and total hip BMD, and suggested that protein intake above current RDI may reduce hip fracture risk and play a beneficial role in BMD maintenance in older adults.[12,13]

Older people commonly have decreased skeletal muscle mass and strength from reduced production of muscle tissue.[14] Because protein intake plays an integral part in muscle and bone health, an intake of 1.0–1.2g/kg body weight per day has been recommended for older adults.[15]

A recent Australian study assessing the effectiveness of a nutritional intervention in institutionalised older adults by improving calcium and protein intake (<1 g/kg body weight protein per day) using dairy foods showed an 11% reduction in the risk of falls, a 48% reduction in hip fractures, and a 30% reduction in all fractures.[16]

Vitamin D

Vitamin D has an important role in maintaining bone health by promoting calcium absorption and bone mineralisation.[17] Epidemiological evidence using serum 25 hydroxyvitamin D (25(OH)D) as a measure of adequate vitamin D status has reported that ‘an estimated 31% of adults in Australia have inadequate vitamin D status (25(OH)D <50 nmol/L), increasing to more than 50% in women during winter–spring and in people residing in southern states’.[18]

A major source of vitamin D in Australia is sunlight exposure, especially in summer.[19,20] However, after the age of 70 years, the skin is thinner and may be less efficient at synthesising adequate amounts of vitamin D,[21] although adequate vitamin D synthesis is seen if doses of ultraviolet (UV) radiation exposure are not too high.[22] A much bigger issue is a tendency for older people to avoid going, or not be able to get, outdoors.[23]

UV radiation from the sun has both beneficial and harmful effects on human health.[24] A balance is required between excessive sun exposure that increases the risk of skin cancer and enough exposure to maintain adequate vitamin D levels. Consider a patient’s risk of skin cancer when considering sun exposure advice:

- People with a high risk of skin cancer (those with very pale skin and/or olive/pale brown skin

with other risk factors) are advised to adopt a very cautious approach to sun exposure when the UV index is ≥3.[24]

- In Australia, for people with an intermediate risk of skin cancer (olive or pale brown skin with no other risk factors), sun protection is important but it should be balanced with spending sufficient time outdoors with ample skin exposed to avoid vitamin D deficiency.[24] How much time outdoors depends on many factors, including skin surface area exposed, skin tone and latitude (which makes a difference, particularly in winter). As a rough guide for most people with olive or pale brown skin, exposure of approximately 15% of body surface (ie hands, face and arms) for 5–10 minutes on most days of the week in summer around mid-morning and mid-afternoon should maintain vitamin D levels.[18]
- For those with constitutively dark skin, who are at low risk of skin cancer but need higher doses of UVB to make adequate vitamin D, sun protection measures are not needed unless spending extended times outdoors when the UV index is ≥3.[24]

Sun exposure in winter should be with as much skin uncovered as practical, considering external temperature, and during the middle of the day, if possible.[18,24] Tables showing approximate exposure times for different seasons, skin colours, latitudes and clothing styles (shorts and T-shirt or long sleeves and long pants) are available.[24] Sunscreen use blocks vitamin D synthesis in the laboratory, but does not have a major effect in practice on vitamin D status; time in the sun and surface area exposed are more important.[24] Body fat is also relevant because obesity is associated with less vitamin D synthesis with vitamin D distribution into fat stores, resulting in lower blood levels of 25(OH)D.[25]

The current RDI of vitamin D in Australia in individuals aged >50 years is 400 IU (10 mcg) per day, rising to 600 IU (15 mcg) per day in those aged >70 years.[26,27] Useful amounts of vitamin D3 can be acquired through food, such as canned salmon, which has approximately 19 mcg (770 IU) vitamin D3 per 100 g, fresh Atlantic salmon (~5 mcg [200 IU] vitamin D3 per 100 g) or fresh white fish (up to 3.5 mcg [140 IU] vitamin D3 per 100 g).[3] These new data suggest that fish may be a useful source of vitamin D, particularly during winter.[21]

Calcium and vitamin D supplementation

There is a large body of evidence to support the role of calcium and vitamin D in the maintenance of bone health.[8,28] The role of calcium and vitamin D supplementation in the treatment of osteoporosis has also been extensively studied in clinical trials. Although calcium and vitamin D supplements have been widely used to prevent bone loss and fractures in postmenopausal women and older men, the use of these supplements continues to be controversial, with studies indicating both no significant association[1] and reduced fracture risk.[29] However, these studies were mostly in healthy, non-institutionalised individuals with limited participants who had low baseline vitamin D status.

Evidence indicates that the absolute benefit of these treatments in terms of short-term (less than five years) fracture prevention for non-institutionalised individuals is relatively low and considerably less than that seen with licensed osteoporosis treatments, such as bisphosphonates or denosumab.[8,29] The US Preventive Services Task Force has recommended against routine calcium and vitamin D supplementation in non-institutionalised older people.[30] However, there is reasonable evidence of benefit for those who may be deficient, particularly institutionalised individuals or frail older people.[31]

Based mainly on calcium balance studies, the target calcium intake from dietary sources and supplements should be 1000 mg per day for adults, rising to 1300 mg per day for women aged >50 years and men aged >70 years.[3,8,32] Vitamin D from sunlight exposure (with more sun protection and limited time outdoors for people at high risk of skin cancer and less protection and more time outdoors for those with dark skin at low risk of skin cancer[24]) or, if sun exposure is very limited, supplements should ensure serum 25(OH)D concentrations >50 nmol/L.[8] Although the middle of the day has the highest UV overall, so skin damage may occur in a very short time, it is also when the ratio of UVB (needed for vitamin D synthesis) to UVA (which damages the skin and does not produce vitamin D) is highest.[17,24]

If vitamin D supplements are required to achieve target serum 25(OH)D concentrations of >50 nmol/L as recommended,[8] a dose of 800–1000 IU per day is usually sufficient, although higher doses are needed in some people.[17,18,28] Dietary calcium intake is often suboptimal in older people, especially institutionalised individuals.

Calcium and vitamin D supplements work together by reducing secondary hyperparathyroidism and bone turnover. BMD is also increased by calcium and vitamin D, but this effect appears modest. Calcium and vitamin D are not available on the PBS, but are recommended for people likely to have insufficient intakes. This is particularly important for those taking other osteoporosis therapies.

Calcium supplements are available in two common forms: calcium carbonate and calcium citrate. Calcium tablets typically contain 250–600 mg of elemental calcium. The most commonly available type of vitamin D supplement is vitamin D3 or cholecalciferol. Vitamin D3 elevates serum 25(OH)D concentrations more than vitamin D2 or ergocalciferol and is more reliably measured by commercially available assays. Currently available doses of vitamin D range from 400 to 1000 IU, available as capsules, tablets or liquid formulations.

Side effects and potential harms

Calcium supplements modestly increase the risk of renal calculi.[39] Calcium supplements can also cause abdominal bloating and constipation.[39] It has been reported there could be an increased risk of myocardial infarction with calcium supplements,[40] but not all studies support this conclusion.[41] Calcium and vitamin D supplements do not increase the risk of death and some studies suggest a small reduction in the risk of death.[41]

Clinical toxicity is uncommon with vitamin D, even at high doses. Single doses of up to 500,000 IU are tolerated without causing hypercalcemia or hypercalciuria. However, the use of higher-dose formulations of vitamin D in older people has been associated with an increased risk of falls. Overall, daily, or at most, weekly vitamin D supplements are preferred.[31]

Evidence Statement

The benefit of vitamin D and/or calcium supplementation on fracture prevention has been extensively assessed in numerous clinical trials with varying protocols, with a significant number of systematic reviews and meta-analyses reporting different conclusions.[29,33–35] A Cochrane review of vitamin D in postmenopausal women and older men,[36] as well as several other reviews,[29,31,33,34,37] concluded that although vitamin D alone is unlikely to prevent fractures in the doses and formulations tested so far in older people, supplements of vitamin D with calcium may prevent hip or other type of fracture. A 2022 comprehensive umbrella review assessing reasons for the discrepancies among systematic reviews/meta-analyses of trials (generally of less than five years) on vitamin D supplementation concluded that although calcium and vitamin D supplements together reduce the risk of hip and other fractures, this seemed largely due to data from institutionalised individuals, despite there being no significant differences in relation to residency in subgroup analyses.[31] Overall, the reductions in fracture risk with vitamin D and calcium from these trials are small in absolute terms with relatively large numbers of people needed to be treated to prevent fractures. Only the Cochrane review[37] was deemed by the umbrella review to be of moderate quality.[31]

A recent ancillary study of the randomised controlled Vitamin D and Omega-3 Trial (VITAL) involving 28,871 participants with mean age of 67 years reported that vitamin D3 supplementation (2000 IU per day) alone did not result in a significantly lower risk of fractures than placebo among generally healthy mid-life and older adults with generally good vitamin D status.[38] These recent findings importantly question the health benefits of vitamin D supplements alone in the general population of older adults, although as the authors of the VITAL study state, the study was not designed to investigate people with low vitamin D status and there were not enough participants with low vitamin D to draw any conclusions for them.[38] RCTs are necessarily conducted over a few years only and with limited exceptions, such as those involving subjects in aged care facilities, generally enrol people of good enough health and mobility to participate in the trial process. Vitamin D and calcium are both threshold ‘nutrients’, meaning that giving more to people who already have enough, however defined, cannot be expected to have a benefit.[28]

A recent study regarding improving nutrition in aged care settings that included increasing calcium and protein intake levels in people who were vitamin D replete have shown benefits such as fall and fracture reduction.[16]

A very large body of evidence, including the 662-page 2011 Institute of Medicine report[8] and other reviews,[28] points to a causal role of vitamin D and calcium for bone health. Severe vitamin D and/or calcium deficiency is the cause of most cases of rickets and osteomalacia.[8,28] Deficiency of either calcium or vitamin D can accelerate bone loss and osteoporosis in older people due to increases in parathyroid hormone and secondary hyperparathyroidism.[8,17,28]

The safety of calcium and/or vitamin D supplements has also been examined in several meta-analyses.[37,39,40] In a Cochrane review, the risk of renal insufficiency or calculi was found to be increased by vitamin D and calcium supplements (RR 1.17; 95% CI: 1.03–1.34).[39] That review also found an increased risk of gastrointestinal symptoms with vitamin D and calcium supplements (RR 1.04; 95% CI: 1.00–1.08).[39] The risk of cardiac events has also been examined, but despite being based on datasets from the same RCTs, different meta-analyses have drawn different conclusions. One meta-analysis found an increased risk of myocardial infarction (RR 1.24; 95% CI: 1.07–1.45) and stroke (RR 1.15; 95% CI: 1.00–1.32) in people taking calcium supplements with or without vitamin D;[40] another meta-analysis found no association with myocardial infarction (RR 1.08; 95% CI: 0.92–1.26) or coronary heart disease in general.[37] Meta-analyses generally indicate that calcium supplements with or without vitamin D have no effect on overall mortality, but the combination of calcium and vitamin D has been found to reduce the risk of death in one meta-analysis.[41]

RCTs have evaluated the effectiveness of higher-dose intermittent vitamin D supplements to reduce the risk of falls in individuals at high risk of falling. The use of high-dose oral vitamin D increased the risk of falls rather than reduced it.[42,43] One trial that compared the effect of 24,000 IU vitamin D once per month to 60,000 IU vitamin D once per month found that the higher dose was associated with a significantly increased incidence of falls.[43]

Practical tips and precautions

- In otherwise healthy non-institutionalised individuals, the relative reduction in fracture risk with calcium and/or vitamin D supplementation alone is small and may be associated with some adverse events. As such, these should not be considered routinely in healthy people or as first-line treatments for people with osteoporosis.
- Nevertheless, in adults, adequate calcium intakes of around 1000 mg per day from dietary sources and vitamin D from sunlight exposure, except in people with a high risk of skin cancer, to maintain 25(OH)D concentrations above 50 nmol/L should be encouraged. Short, frequent exposures are efficient for most people, with longer exposures for those with dark skin.
- In frail or institutionalised older individuals, target calcium intake should be 1300 mg per day in postmenopausal women and men aged >70 years, ideally from dietary sources. Where this cannot be achieved, a calcium supplement of 500–600 mg per day is suggested.[23]
- In frail or institutionalised older individuals, some sunlight exposure (with short, frequent exposures being more efficient for most people and longer exposures for those with dark skin) if practical and/or supplements should ensure that serum 25(OH)D concentrations are above 50 nmol/L.[23]
- A protein target intake of 1.0–1.2 g/kg body weight per day could be considered for frail and institutionalised people. Increased dairy intake could help achieve calcium and protein targets.
- Calcium citrate does not need to be taken after meals like calcium carbonate because it does not require an acid environment to be optimally absorbed. Calcium and vitamin D supplements

may be taken at any time of the day.

- Calcium and vitamin D supplements are more likely to be effective in reducing fracture risk when given in combination to individuals who are deficient. Most studies demonstrating efficacy of other osteoporosis treatments have been conducted in the setting of concurrent calcium and vitamin D supplementation (i.e., in calcium- and vitamin D-replete people).

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Reducing falls

Reducing falls

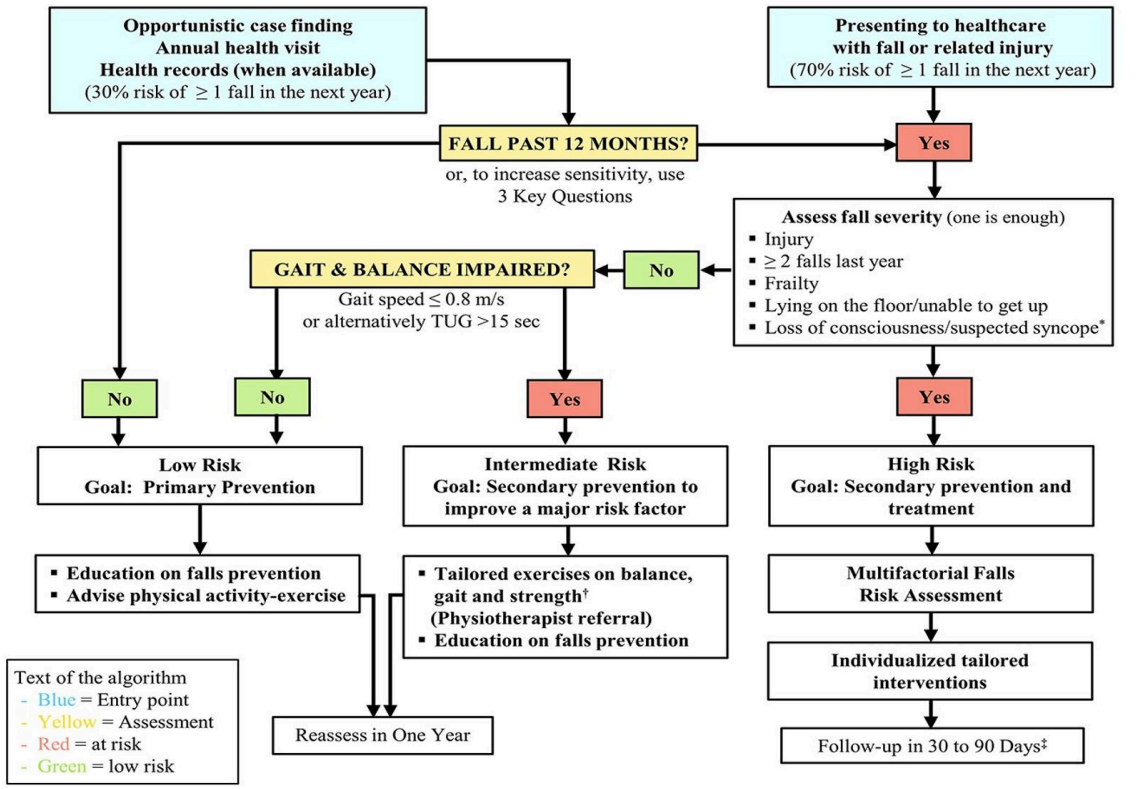
Recommendations

Recommendation 15	Grade
Opportunistic case finding should be undertaken as per the recommended algorithm (**Figure 1**) to identify older people at risk of falls and fall-related injury.[1]	A
Recommendation 16	**Grade**
Offer further assessment and/or interventions to prevent falls based on the level of risk identified.	A

Most people who sustain peripheral fractures do so after a fall. There is strong evidence that a range of interventions significantly reduce falls when targeted at the right populations,[1–8] and that fall prevention exercise programs significantly reduce fall-related injuries, including fractures.[2–8] A systematic approach identifying people at risk of falling, assessing for modifiable risk factors and implementing strategies to reduce this risk is likely to reduce the risk of fractures.[9]

Opportunistic case finding and assessment for falls risk

The world falls guidelines provide a simple algorithm (**Figure 1**) to guide clinicians in identifying and assessing the risk of falls in an older population.[1]



Notes: 3 Key Questions (3KQ) any positive answer to a) Has fallen in the past year? b) Feels unsteady when standing or walking? or c) Worries about falling? prompts to "fall severity" step. **Fall severity**: fall with injuries (severe enough to consult with a physician), laying on the ground with no capacity to get up, or a visit to the emergency room, or loss of consciousness/suspected syncope. **Frailty.** Commonly used frailty assessment tools include the Frailty Phenotype and the Clinical Frailty Scale.
*Syncope suspicion should trigger syncope evaluation/management. †Exercises on balance/leg strength should be recommended for the intermediate group. Evidence shows that challenging balance exercises are more effective for fall prevention. In several settings, this intermediate group is referred to a physiotherapist. ‡ High risk individuals with falls can deteriorate rapidly, and close follow up is recommended and should be guided on the frequency of consequent health service utilization. **TUG:** timed up and go test

Figure 1. World falls guidelines algorithm for the identification and assessment of falls risk.

Figure 1.[1]

Reproduced from Montero-Odasso M, van der Velde N, Martin F, Petrovic M, et al. World guidelines for falls prevention and management for older adults: a global initiative. Age and ageing 2022; 51(9):1-36, with permission from Oxford Academic.

Using the information derived from the algorithm, people are classified as at 'low', 'intermediate' or 'high' risk of falls and fall-related injury. Strategies to reduce the risk of falls are then tailored to the level of risk as outlined below:

- Older adults at low risk for falls, who should be offered education about falls prevention and exercise for general health and/or fall prevention.
- Older adults at intermediate risk for falls, who, in addition to the above, should be offered targeted exercise or a physiotherapist referral to improve balance and muscle strength, and reduce fall risk.
- Older adults at high risk for falls, who should be offered a multifactorial falls risk assessment to inform individualised tailored interventions.[1]

Gait speed or the timed up and go test are recommended as screening tools for gait and balance problems.[1] Gait speed is a simple measure of distance over time, but requires sufficient space (the usual distance covered is six metres) to undertake the test. The timed up and go test measures the

time taken for an older person to get up from a chair without using their arms, walk three metres, turn, return to the seat and sit down. A time of >15 seconds may indicate an increased fall risk, but it is important to assess gait quality and transfers in addition to time taken to complete the task.[10]

Those identified as at high risk of falls require a multifactorial assessment and tailored intervention based on the risk factors identified. This assessment may include tests of vision (including types of glasses worn), strength, balance and postural hypotension, as well as a review of medications and the identification of neurological and cognitive deficits. Attention should be paid to foot care and footwear. The information derived from this multidomain assessment should be used to formulate an intervention and management plan in partnership with the older person.

Evidence Statement

A Cochrane review found multifactorial interventions, which include individual risk assessment, reduced the rate of falls in community-living older people by 23% (rate ratio [RaR] 0.77; 95% CI: 0.67–0.87; 19 trials; 5853 participants).[4] A companion Cochrane review found exercise (all types) reduced the rate of falls by 23% (RaR 0.77; 95% CI 0.71–0.83; 59 trials; 12,981 participants).[2] In terms of optimal exercise modalities, balance and functional exercise programs reduced the rate of falls by 24% (RaR 0.76; 95% CI 0.70–0.81; 39 trials; 7920 participants) and multiple type exercise programs (most commonly balance and functional exercises plus resistance exercises) reduced the rate of falls by 34% (RaR 0.66; 95% CI 0.50–0.88; 11 trials; 1374 participants).[2] Exercise may also reduce the number of people experiencing one or more fall-related fractures (RR 0.73; 95% CI 0.56–0.95; 10 trials; 4047 participants).[2] An RCT of home-based interventions teaching principles of balance and strength training and integrated selected activities into everyday routines (Lifestyle-integrated Functional Exercise [LiFE] program) reduced the rate of falls by 31% (RaR 0.69; 95% CI: 0.48–0.99).[11]

Home-safety assessment and modification interventions have been shown to reduce the rate of falls (RR 0.81; 95% CI: 0.68–0.97; six trials; 40,208 participants).[5] These interventions have been most effective in people at higher risk of falling, including those with a recent fall-related hospital admission, and when implemented by an occupational therapist. When regular wearers of multifocal glasses (597 participants) were given single-lens glasses, both inside and outside falls were significantly reduced in the subgroup that regularly took part in outside activities. Conversely, there was a significant increase in outside falls in intervention group participants who took part in little outside activity. Pacemakers reduced the rate of falls in people with carotid sinus hypersensitivity (RR 0.73; 95% CI: 0.57–0.93; three trials; 349 participants). First eye cataract surgery in women reduced the rate of falls (RR 0.66; 95% CI: 0.45–0.95; one trial; 306 participants), but second eye cataract surgery did not.[5] A systematic review found that strategies to deprescribe 'fall risk-increasing drugs' (primarily psychotropic drugs) did not significantly reduce the rate of falls (RaR 0.98; 95% CI 0.63–1.51; five trials; 1309 participants).[6] One trial (305 participants) in people with disabling foot pain found that multifaceted podiatry, including foot and ankle exercises, significantly reduced the rate of falls compared with standard podiatry (RR 0.64; 95% CI: 0.45–0.91).[4]

In a Cochrane review of fall prevention interventions for people residing in residential aged care facilities that included 95 trials (138,164 participants),[6] the primary findings were that the following interventions probably make no, or little, difference to the rate of falls: exercise (RR 0.93; 95% CI: 0.72–1.20; 10 trials; 2002 participants); general medication reviews (RR 0.93; 95% CI 0.64–1.35; six trials; 2409 participants); and multifactorial

interventions (RR 0.88; 95% CI 0.66–1.18; 10 trials; 3439 participants). Vitamin D supplementation probably reduces the rate of falls in residents of aged care facilities (RR 0.72; 95% CI 0.55–0.95; four trials; 4512 participants).[12]

Finally, one Australian trial,[13] published since the Cochrane systematic review,[6] found strength and balance exercise reduced falls by 55% (incidence rate ratio 0.45; 95% CI: 0.17–0.74) in residents of aged care facilities.

Practical tips and precautions

- Develop a plan to reduce fall and fracture risk in partnership with the older person to maximise uptake and adherence to recommendations.
- Exercise is the most evidence-based intervention and has been shown to prevent falls in both older people at increased risk and the general population of older people. Except for those with specific contraindications, exercise should be recommended for all older people. Both home- and community-based exercise programs are effective in preventing falls, but in both cases the exercises need to include medium- to high-intensity balance training (ie exercises must be undertaken while standing and challenge balance) and be of long duration, preferably ongoing[2,3] (see **Section 2.3**).
- Ensure medications are reviewed on a regular basis and that medications known to increase falls are avoided or prescribed at the lowest dose and for the shortest possible time.
- Refer people with painful feet or foot deformities that increase falls risk to podiatry for intervention.
- Provide advice on the dangers of bifocal and multifocal glasses when walking outdoors (blurring of ground-level obstacles) and recommend the wearing of single-lens glasses when outdoors.
- Identify cataracts and refer for cataract extraction.
- Refer people with a history of recent falls for an occupational therapy home assessment.
- Assess for and treat postural hypotension and cardiovascular disorders.

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Exercise

Exercise

Specific modalities of exercise have a preventive and therapeutic role to play in modifying both skeletal and non-skeletal risk factors for osteoporosis and osteoporotic fracture.

Progressive resistance training (also known as strength training or weightlifting) is an exercise modality in which muscles are exposed to a progressively greater load against a resistance (e.g., one's own body weight or an external resistance such as free weights) and, in contracting to oppose this load, adapt by growing in size and strength. The muscle contractions and adaptations that occur create tension (strain) on bones that are associated with beneficial adaptations in bone density at skeletal sites attached to the trained muscle groups.

Weight-bearing impact exercises, which involve the skeleton supporting the weight of the body ('load') with an additional force (impact) imparted through the skeleton (e.g., jumping), are also an effective way to load and stimulate bones to maintain or increase bone density, structure, and strength.

Balance training in isolation does not improve BMD, although, if challenging, can reduce falls risk (refer also to **Section 2.2**). Other kinds of exercise, such as walking and non-weight-bearing activities (e.g., cycling and swimming) have minimal effects on BMD and no significant effects on falls risk in RCTs, and may increase (e.g., walking) the risk of fracture, especially in those with poor balance, frailty, and sarcopenia.

Recommendations

Recommendation 17	Grade
Exercises recommended to reduce fracture risk: • Muscle resistance (strength) training should be regular (at least twice a week), moderate–vigorous and progressive. • Weight-bearing impact exercises should be performed most days (at least 50 moderate impacts) and include moderate-to-high loads in a variety of movements in different directions. • Balance training activities should be challenging. Limit prolonged sitting (sedentary behaviour).	B
Recommendation 18	**Grade**

Exercise programs for very frail older institutionalised people and those with a high vertebral fracture risk should be supervised, modified and tailored to minimise the potential to increase the risk of falls, injury and vertebral fractures.	C
Recommendation 19	**Grade**
Prescribe extended and supervised exercise therapy, including targeted resistance and challenging balance training, after hip fracture to improve mobility, strength and physical performance and to reduce the risk of falls.	B
Recommendation 20	**Grade**
Evidence for the benefits of exercise after vertebral and non-hip fractures is limited, but suggests supervised resistance training will build bone once a fracture has healed to the same extent as in non-fractured patients. For people with a vertebral fracture, exercises to strengthen back muscles, enhance flexibility and improve posture, as well as to reduce falls risk, should be considered.	D

Exercise for increasing or maintaining bone mass

Moderate- to high-impact weight-bearing activities (jumping, hopping) and progressive resistance (strength) training are most effective for increasing or maintaining BMD.[1–4] There is minimal evidence of benefit for low-intensity resistance or low-impact weight-bearing aerobic exercises, such as walking and cycling.[4,5] High-velocity resistance training (or power training), in which the concentric (pushing) phase of the exercise for lower limb exercises is performed rapidly, has been shown to provide further benefit to BMD when added to traditional resistance training and to improve lower limb muscle power.[6,7] Muscle power represents the ability of muscle to produce force quickly and this form of training can not only stimulate bone adaptation via rapid muscle contractions, but also reduce falls risk since it can improve movement speed (e.g., ability to step quickly when balance is perturbed). Moderate- to high-impact exercises, such as jumping, may be considered where the risk of fracture is low (e.g., in people without osteoporosis) and there are no contraindications (e.g., joint problems, severe balance impairment). Examples of weight-bearing impact exercises which are moderate-to-high impact that may benefit BMD and strength, include marching/stomping, stair climbing, jumping, hopping, dancing, tennis, basketball, and netball.

The dose (volume) of exercise required to elicit skeletal adaptations is specific to the modality and intensity of the exercise chosen. Short, intermittent bouts of moderate- to high- impact weight-bearing exercise (1-2 minute bouts that include 50 impacts e.g., 5 sets of 10 impacts per session) are more

beneficial to increase or maintain BMD than one longer, less-intense or low-impact session.[8,9] Weight-bearing impact exercises should be performed on most days of the week and include multidirectional or diverse movements to stimulate bone adaptation.[9] Resistance training requires two to three sets of 8–10 repetitions at moderate to high intensity (progress to 70–85% of peak muscle strength) that include exercises targeting major muscle groups attached to the hip and spine (about eight exercises per session) and performed at least twice per week.[9] Resistance training may be prescribed using machines or free weights in which the loads (weights) are increased progressively over time. This is referred to as 'progressive overload', a critical training principle to elicit skeletal adaptations over time. For optimal skeletal benefits, progressive resistance training should be performed in combination with moderate- to high-impact exercises.[1,3,10]

Exercise to promote balance and prevent falls

Exercise for preventing falls needs to include high challenging balance and functional training (e.g., exercises should be undertaken while standing and challenge balance; that is, place the person at the edge of their balance or functional ability, and incorporate activities relevant to everyday functional tasks).[11,12] The greatest benefits in reducing falls risk are observed following individualised and supervised programs that include stepping and multimodal balance and functional training programs performed two to three times per week (dose of ≥3 hours per week) for at least four months.[12] Examples of challenging balance exercises include standing with the feet close together, standing on one leg, tandem walking, figure-8 walking, stepping exercises, backwards or sideways walking, 'exergames' and tai chi. Effective programs have been designed so that older people can undertake balance training safely unsupervised at home or in centre-based classes.

Caution is advised to avoid or minimise rapid, repetitive, weighted and end-range forward flexion or twisting of the spine in those with spinal osteoporosis or a history of vertebral fractures. In people with spinal osteoporosis or a history of vertebral fractures, emphasis should be placed on exercises to strengthen back muscles (focusing on muscle endurance at a low intensity) to improve posture and support the spine. Challenging balance training should be undertaken in safe settings, initially under supervision. Important muscle groups to target include back extensors, abdominals, shoulder stabilisers, triceps, hip extensors, hip abductors, knee extensors, plantar and dorsiflexors.

The goals of exercise in the treatment of osteoporotic hip fracture focus on the modifiable, non-skeletal contributors to weakness, frailty, falls and functional dependency, including muscle strength and power, balance, gait stability, poor appetite, depression, cognitive impairment, social isolation, and polypharmacy (e.g., by substituting exercise for sedatives and antidepressants).

Exercise to reduce fractures

Evidence Statement

Specific kinds of exercise maintain BMD or reduce bone loss associated with ageing and menopause. The effects of exercise on BMD are modest and site specific.[4,8] The most effective exercises include high-force, high-velocity, moderate- to high-impact, intermittent stimuli and novel directions of movement involving muscles that are attached to bones susceptible to fragility fracture (vertebrae, hip, femur, pelvic, ankle, wrist). Multimodal exercise programs that include progressive resistance training combined with moderate- to high-impact weight-bearing exercise generally provide the greatest skeletal benefit in older adults.[1–4,8] Non-weight-bearing aerobic activities such as swimming and cycling may be associated with low BMD.[13] Simple walking does not prevent bone loss, osteoporosis or fracture.[5] In fact, walking alone has been shown to increase fracture risk in postmenopausal women and men.[14,15] Lower-intensity resistance training or low-impact training is less effective for eliciting beneficial skeletal effects at the hip and spine.[2]

Although fracture has been the primary outcome in few exercise RCTs to date, there is evidence from several reviews and meta-analyses[16–19] that exercise may reduce the risk of osteoporotic fracture, particularly if it includes resistance training or multimodal robust exercise regimens.

No exercise regimens have been shown to reduce recurrent hip fracture. There is evidence that extended exercise therapy added to usual care is safe and effective after hip fracture, and results in improved mobility, strength and physical performance.[20,21] Exercise may play a role both in rehabilitation from the osteoporotic fracture itself and in the prevention of additional fractures, and is often combined with other multidisciplinary care strategies.[20] High-intensity progressive resistance training, in combination with other treatments for frailty and mobility impairment, such as balance training, nutritional support and treatment for depression, has resulted in reduced nursing home admission and overall mortality in a hip fracture cohort,[22] as well as improved strength, nutritional status and depressive symptoms. In contrast, various hip fracture rehabilitation strategies that included no exercise or only low-intensity exercise have had mixed or minimal impact on short- or long-term rehabilitative outcomes.[23,24]

Robust data on exercise after vertebral fracture are limited. A Cochrane review of nine trials in individuals with a history of vertebral fracture reported insufficient evidence to determine the effects of exercise on incident fractures, falls or adverse events, but there was some moderate-quality evidence that exercise can improve physical performance and very-low-quality evidence (data from some individual trials) reporting benefits for pain and quality of life.[25] An earlier systematic review of nine trials also reported modest benefits of exercise for strength and balance without increases in pain, but no consistent or high-quality evidence for quality of life, BMD, recurrent fractures or other outcomes.[24] There is some evidence that physiotherapy and exercise after upper extremity fracture may reduce

pain and upper limb function,[26] although few high-quality trials exist. A systematic review of 31 controlled trials of exercise after ankle fracture reported that commencing exercise after surgery in a removable brace or splint significantly improved activity limitation, but also led to a higher rate of adverse events (RR 2.61; 95% CI: 1.72–3.97), whereas most other approaches were ineffective.[27]

Practical tips and precautions

- The most important components of the exercise prescription for the prevention of osteoporosis are moderate- to high-intensity progressive resistance training in combination with weight-bearing impact exercise and challenging balance training.
- Exercise programs should be individualised to a person's needs, abilities and interests. People with osteoporosis should be encouraged to 'do more' and not 'less' in terms of exercise. It is important that healthcare professionals adopt a positive and encouraging approach to exercise that does not create a sense of fear.
- Particularly when the individual has not undertaken recent physical activity, exercise programs should commence at a low level and be continuously progressive to reach target volumes and intensities as muscle strength and function improve. A physiotherapist or exercise physiologist can assist in developing the most appropriate program, providing education on safe and effective training techniques, increasing motivation and ongoing monitoring of benefits.
- Limiting rapid, repetitive, weighted and end-range forward flexion or twisting of the spine during daily activities and the inclusion of back extension strengthening exercises may minimise the risk of vertebral fractures, as well as exacerbation of pain from spinal osteoarthritis. In the presence of existing spinal osteoporosis or vertebral fracture, it is important to provide clear instructions and advice on safe and correct lifting techniques for day-to-day moving and when lifting, moving and transitioning in and out of exercises.
- Avoid flexion and internal rotation movements in those with a total hip replacement.
- Individuals with arthritis may need to modify exercises in terms of modality, intensity, range of motion or extent of weight-bearing exercise to prevent exacerbation of joint symptoms. Seated resistance training exercise is preferable to weight-bearing aerobic exercise or higher-impact activities for bone health in those with significant degenerative joint disease or instability, at least until joint and muscle health is improved or stabilised.
- To reduce falls risk, prescribe challenging balance or multimodal programs that include resistance training prior to promotion of ambulation if gait and balance are impaired.
- Optimise lighting, visual and hearing aids, safety of the exercise environment, climate conditions and footwear in all exercise settings and exercise at times of day when sedation from medications or fatigue are at a minimum and cognition and mood are optimal.

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Pharmacologic approaches to prevention and treatment

Pharmacologic approaches to prevention and treatment

Pharmacological approaches to prevention and treatment may be divided as follows:

- antiresorptive therapy (inhibits osteoclast activity)
    - bisphosphonates (eg alendronate, risedronate, zoledronate/zoledronic acid)
    - denosumab
    - menopausal hormone therapy (eg oestrogen, tibolone)
    - selective oestrogen receptor modulators (SERMs; eg raloxifene)

- osteoanabolic therapy (predominant stimulatory effect on osteoblasts)
    - teriparatide
    - romosozumab (also inhibits osteoclast activity).

Bisphosphonates

Bisphosphonates

Recommendations

Recommendation 21	Grade
Bisphosphonate therapy (alendronate, risedronate or zoledronate) should be considered for the primary prevention of vertebral fractures in women with osteopenia who are at least 10 years postmenopause.	B
Recommendation 22	**Grade**
Bisphosphonate therapy is recommended for reducing the risk of vertebral and non-vertebral fractures in postmenopausal women and men over the age of 50 years at high risk of fracture (those with osteoporosis by BMD criteria, or prior minimal trauma fracture).	A (women) C (men)
Recommendation 23	**Grade**
Reconsider the need to continue bisphosphonate therapy after 5–10 years in postmenopausal women and men over the age of 50 years with osteoporosis who have responded well to treatment (T-score ≥−2.5 and no recent fractures). If BMD remains low (T-score ≤−2.5) and/or there are incident fragility fractures, continue treatment. Treatment should be restarted if there is bone loss, especially at the hip, or if a further minimal trauma fracture is sustained.	D

Bisphosphonates are potent inhibitors of bone-resorbing cells (osteoclasts). They work to inhibit bone resorption by interfering with normal osteoclast function and inducing osteoclast cell death (apoptosis). Because bisphosphonates are rapidly sequestered into bone (from where they are slowly released) and eliminated by the kidney, exposure to soft tissues, including bone marrow, is transient.

Alendronate and risedronate are taken orally once weekly. A monthly oral risedronate preparation (150 mg) is also available, although some patients find this too infrequent and may forget to take it. Intravenous (IV) bisphosphonates (once yearly; 5 mg zoledronate/zoledronic acid) can be used as first-line osteoporosis therapy and are often used in patients intolerant of oral preparations or likely to be non-adherent to oral medications. IV zoledronate has been shown to reduce mortality following hip fracture[1] and to reduce fractures in the presence of osteopenia (hip T-scores between −1.0 and −2.5) without a fracture.[2] Further analysis from the same study has intriguingly found that in women with osteopenia, zoledronate was associated with fewer myocardial infarcts (RaR 0.58; 95% CI: 0.35–0.94) and cancers (RaR 0.68; 95% CI: 0.52–0.89).[3] Although these findings need to be confirmed in larger studies, they suggest potential non-skeletal benefits of zoledronate.

Side effects and potential harms

Bisphosphonates used in the management of osteoporosis are usually well tolerated. The most commonly reported adverse effects are gastrointestinal (gastric irritation, oesophageal erosions, gastric ulcers, perforations, and strictures). According to one meta-analysis,[4] oral bisphosphonate therapy may be associated with oesophageal cancer risk; however, this has not been found in two other meta-analyses.[5,6] Medication-related osteonecrosis of the jaw (MRONJ) is a rarely reported adverse effect (refer to **Section 5.3**). The incidence of MRONJ is in the range <1–10 cases per 10,000 patients treated with oral bisphosphonates[7,8] and 1.7 cases per 10,000 patients treated with zoledronic acid.[9]

Atypical fracture of the femur (AFF) also appears to be a rare adverse event, occurring at a rate of 3.2–50 cases per 100,000 person-years of bisphosphonate treatment[10] (refer to **Section 5.4**). In a recent North American study, 196,129 women aged >50 years receiving bisphosphonates were followed for 10 years.[10] The risk of AFF increased with longer duration of bisphosphonate use – compared with a treatment duration of less than three months, the hazard ratio (HR) for treatment duration of three to less than five years was 8.86 (95% CI: 2.79–28.20), and this increased to 43.51 (95% CI: 13.70–138.15) for treatment for eight years or more.[10] Other risk factors were race (HR for Asian versus White 4.84; 95% CI: 3.57–6.56), decreasing height (HR per 5-cm decrement 1.28; 95% CI: 1.15–1.43), increasing weight (HR per 5-kg increment 1.15; 95% CI: 1.11–1.19), age (HR for age 65–74 versus >85 years 2.76; 95% CI: 1.62–4.72) and glucocorticoid use for 1 year or more (HR versus no glucocorticoid use 2.28; 95% CI: 1.52–3.43). Reassuringly, bisphosphonate discontinuation was associated with a rapid reduction in AFF risk and the absolute risk of AFF remained very low (1.74 fractures per 10,000 patient-years) compared with reductions in the risk of hip and other fractures with bisphosphonate treatment. For example, after three years, there were two bisphosphonate-associated AFF, compared with 149 hip fractures prevented and 541 clinical fractures prevented.[10] The benefit-to-risk ratio of bisphosphonate use for osteoporosis treatment is therefore very favourable.

Concern has been raised about bisphosphonate use around the time of fracture due to inhibition of bone remodelling. The Fracture and Bisphosphonates trial was a double-blind placebo-controlled trial involving 15 trauma centres in the UK that randomised 421 bisphosphonate-naïve patients aged >50 years with a distal radius fracture to alendronate 70 mg once weekly (n=215) or placebo (n=206) within 14 days of fracture. Reassuringly, there was no difference in fracture union at four weeks.

Evidence Statement

Several good-quality systematic reviews have found that bisphosphonates (alendronate, risedronate, and zoledronate) reduce fracture risk. Few studies have directly compared different agents or classes of agents used to treat osteoporosis, and hence data are insufficient to determine the relative efficacy or safety of these agents.

Primary prevention of osteoporotic fractures with bisphosphonates

A pivotal systematic review[12] included two RCTs[13,14] that reported the effect of alendronate 10–40 mg per day on fracture risk in postmenopausal women without osteoporosis. Alendronate was not associated with a reduction in the risk of vertebral fracture (RR 0.45; 95% CI: 0.06–3.15) or non-vertebral fractures (RR 0.79; 95% CI: 0.28–2.24) compared with placebo. In one RCT,[13] the mean age was 51.8 years, the mean T-score −1.8, and no patients had prevalent vertebral fractures; in the other RCT,[14] the mean age of participants was 53 years, the mean T-score was −1.8, and <10% of participants had prevalent vertebral fractures. A Cochrane systematic review and meta-analysis in 2008[15] reported a reduction in the risk of vertebral fractures (RR 0.55; 95% CI: 0.38–0.80), but no reduction in non-vertebral fracture risk (RR 0.89; 95% CI: 0.76–1.04) with alendronate therapy in one study (n=4432).[16] In the Cochrane review, the mean T-score was −1.9, mean age was 67.6 years, and no patients had prevalent vertebral fractures.[15] The fact that patients in the latter study[16] were older by 15 years is likely to have contributed to the positive findings.

A meta-analysis of RCTs of risedronate[17] in postmenopausal women (n=111 in one trial by Mortensen et al[18]) conducted in 2002 did not demonstrate reductions in either vertebral fractures (RR 2.44; 95% CI: 0.12–49.45) or non-vertebral fractures (RR 0.49; 95% CI: 0.12–2.03). A 2008 Cochrane review[19] on the effectiveness of risedronate at doses of 2.5 and 5 mg per day for a duration of two years for the primary prevention of osteoporosis fractures included two RCTs (Mortensen et al[18] and Hooper et al[20]) with 327 early postmenopausal women (mean age 52.6). The results were not significant compared with placebo for either vertebral fracture risk (RR 0.97; 95% CI: 0.42–2.25) or non-vertebral fracture risk (RR 0.81; 95% CI: 0.25–2.58).[19] In the RCTs by Mortensen et al[18] and Hooper et al,[20] the respective mean age was 51.2 and 52.6 years, the mean T-score was −1.0 and −0.4, and 0% and 18% of subjects, respectively, had prevalent fractures.

Treatment of postmenopausal women at high risk of osteoporotic fracture

A good-quality meta-analysis including six treatment trials showed a reduction in the risk of vertebral fracture for alendronate compared with placebo (RR 0.53; 95% CI: 0.43–0.65), with no heterogeneity observed between trials.[12] This translated to a number needed to treat (NNT) of 72 (95% CI: 61–99) to prevent one vertebral fracture over two years of

treatment in women at high risk of vertebral fracture. The patients included were at high fracture risk, as indicated by a weighted mean age of 67.8 years (range 59.5–71 years), weighted mean FN T-score of −2.6 (range −3.3 to −2.3) and a prevalent vertebral fractures weighted mean of 29% (range 0–100%).[12] Among five treatment trials included in the meta-analysis of non-vertebral fracture risk, the weighted mean age was 63.0 years (range 59.5–64 years), the weighted mean FN T-score was −2.7 (range −2.8 to −2.3) and the prevalent vertebral fractures weighted mean was 18% (range 0–21%). The pooled RR for non-vertebral fracture was 0.49 (95% CI: 0.36–0.67), with no heterogeneity between trials. The NNT to prevent one non-vertebral fracture over two years of treatment in women at high risk was 24 (95% CI: 19–37).[12]

A Cochrane review of RCTs in postmenopausal women compared risedronate 2.5 or 5 mg daily to placebo over 2–3 years.[19] These trials were categorised as osteoporosis treatment (or secondary prevention) trials, based upon inclusion criteria of a T-score ≤−2.0 or the presence of a prevalent vertebral fracture. Pooled data from three RCTs showed a 39% reduction in vertebral fractures (RR 0.61; 95% CI: 0.50–0.76) for risedronate 5 mg per day with an estimated NNT of 48. The weighted mean age was 69.1 years (range 64.7–71 years), the weighted mean FN T-score was −2.7 (range −2.9 to −2.4) and the prevalent vertebral fractures weighted mean was 79% (range 30–100%).[19] Pooled data from four RCTs showed a 20% reduction in non-vertebral fractures (RR 0.80; 95% CI: 0.72–0.90), with an estimated NNT of 30. The weighted mean age was 76.9 years (range 64.7–78 years), the weighted mean FN T-score was −3.6 (range −3.7 to −2.4) and the prevalent vertebral age: 42% to 100%. For hip fractures, there was a 26% reduction in risk (three RCTs; RR 0.74; 95% CI: 0.59–0.94), with an estimated NNT of 202. The weighted mean age was 77.3 years (range 69–78 years), the weighted mean FN T-score was −3.6 (range −3.7 to −2.4) and the prevalent vertebral fractures weighted mean was 47% (range 30–100%).[19] The effect observed for 2.5 mg risedronate was not as large.[19]

The multicentre international Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON)–Pivotal Fracture Trial (PFT) followed the safety and efficacy of zoledronic acid in a cohort of postmenopausal women with osteoporosis for nine years. In the initial trial, 7765 patients (mean age 73 years) were randomised to receive either placebo or a single infusion (5 mg) of zoledronate/zoledronic acid at baseline, 12 months and 24 months. At 36 months from baseline, zoledronic acid treatment reduced the risk of morphometric vertebral fracture by 70% compared with placebo (3.3% versus 10.9%; RR 0.30; 95% CI: 0.24–0.38) and reduced the risk of hip fracture by 41% (1.4% versus 2.5%; HR 0.59; 95% CI: 0.42–0.83).[21] A post hoc analysis of data from patients who received only one dose of zoledronic acid at baseline revealed a similar reduction in vertebral fracture risk (68%) at the 18-month follow-up compared with placebo.[22]

Treatment following hip fracture

An annual infusion of zoledronic acid within three months after a hip fracture was associated with a reduction in the rate of new clinical fractures and improved survival in women and men with an average age of 74.4 years, followed for a median of 1.9 years.[1] In that randomised double-blind placebo-controlled trial, rates of any new clinical fracture were reduced by 35% (*P*=0.001) from 13.9% in the placebo group to 8.6% in the zoledronic acid group. The respective rates of a new clinical vertebral fracture in the zoledronic acid and placebo groups were 1.7% and 3.8% (*P*=0.02), and the respective rates of new non-vertebral fractures were 7.6% and 10.7% (*P*=0.03). There was also a reduction of 28% in deaths from any cause in the zoledronic acid group (*P*=0.01).[1] No adverse effects on fracture healing were noted. The rates of renal and cardiovascular adverse events, including atrial fibrillation and stroke, were similar in the two groups.[1] On the basis of that trial, the US Endocrine Society's practice guideline for osteoporosis in men suggested treatment with IV zoledronic acid in men with a recent hip fracture.[23]

Duration of therapy

The Fracture Intervention Trial Long-term Extension (FLEX) trial demonstrated a reduction in clinical (not morphometric) vertebral fractures among those who continued alendronate for 10 years compared with those who discontinued after five years.[24] A post hoc analysis revealed that among postmenopausal women without a vertebral fracture at FLEX baseline, an FN T-score of −2.5 or less at FLEX baseline was associated with non-vertebral fracture risk reduction (RR 0.50; 95% CI: 0.26–0.96).[25] A further post hoc analysis of the FLEX trial showed that among women who discontinued alendronate after five years, the predictors of fracture were age (HR per five-year increase 1.54; 95% CI: 1.26–1.85) and FN T-score (lowest tertile of baseline FN DXA versus the other two tertiles relative HR 2.17; 95% CI: 1.38–3.41).[26] Change in BMD after one year was not a predictor of further fracture.[26]

In an extension of the HORIZON–PFT study, 1233 women who had received three annual doses of zoledronic acid in the original trial were randomised to receive either zoledronic acid for another three years under the same annual, three-dose regimen or placebo.[27] At the 36-month follow-up, the incidence of new vertebral fractures was lower in women who received six years of zoledronic acid than in those who had received the drug for only three years (14 versus 30 fractures; odds ratio [OR] 0.51; *P*=0.035), but there was no change in fracture rate in the placebo group.[27] A further three-year extension of the trial did not show a significant difference in fracture rates between women taking zoledronic acid for a full nine years compared with those who had taken the drug for six years followed by three years on placebo.[28] These results indicate that maximum benefit of zoledronic acid may be achieved in some patients after six years of therapy (for a reduction of vertebral fracture risk) and that for most patients the benefits are maintained for a further three years once therapy is stopped.

Treatment of osteoporosis in men

One RCT found a significant reduction (*P*=0.02) in the risk of vertebral fractures in older men with osteoporosis (n=241) for alendronate 10 mg per day for two years compared with placebo.[29] The effect on non-vertebral fractures was not significant. An RCT to assess the effectiveness of risedronate 5 mg daily versus vitamin D/calcium in men with osteoporosis (n=316) with a baseline mean lumbar spine T-score of −3.3 and a prevalent vertebral fracture rate of 50% found a significant 60% reduction (*P*=0.028) in new morphometric vertebral fractures and statistically significant increases in lumbar spine and hip BMD at one year of follow-up.[30] A placebo-controlled RCT of risedronate involving 284 men over two years with a baseline mean lumbar spine T-score of −3.2 and 25% of subjects with prevalent vertebral fractures demonstrated improved lumbar spine and hip BMD with risedronate.[31] However, there was no significant effect on vertebral or non-vertebral fractures, although the study was underpowered to detect differences in fracture rates.[31] Data on the efficacy of zoledronic acid in reducing fracture risk in men are rare. In a multicentre double-blinded trial of 1199 men with osteoporosis aged 50–85 years and randomised to receive either placebo or 5 mg zoledronic acid at baseline and at 12 months, zoledronic acid reduced the rate of morphometric vertebral fracture by 67% at the 24-month follow-up (RR 0.33; 95% CI: 0.16–0.70; *P*=0.002).[32] The rate of non-vertebral fractures was also lower in the treatment group, but the difference did not reach statistical significance.[32]

Practical tips and precautions

- The bisphosphonates approved in Australia for clinical use in osteoporosis are alendronate, risedronate and zoledronate/zoledronic acid. Alendronate and risedronate (all available preparations) are supported under the PBS for women and men with osteoporotic fracture independent of age, BMD or other clinical risk factors. It is important to note the PBS criteria for osteoporosis pharmacotherapy, namely ‘established osteoporosis with fracture due to minimal trauma’, means that an individual qualifies for subsidised treatment if a minimal trauma fracture has been sustained, regardless of BMD T-score. Assessment of absolute fracture risk and clinical judgement should guide individual decisions on osteoporosis pharmacotherapy.
- Active upper gastrointestinal tract (GIT) disorders (current strictures, Barrett’s oesophagus and gastric, oesophageal or duodenal ulcers) are a contraindication to oral bisphosphonate use.
- The oral bioavailability of bisphosphonates is very low (~1%), so dosing instructions are important. Taking oral therapy after fasting for several hours (usually overnight) and then remaining upright and avoiding food for at least 30 minutes will maximise medication absorption. Enteric-coated risedronate can be taken with or without food, making this formulation very convenient. This may assist with increasing patient medication adherence.
- The incidence of GIT adverse events is low in patients without prior upper GIT disorders and minimised by taking the tablet with a large glass of water and remaining upright until after

eating.

- Calcium and vitamin D intake appropriate for gender, age and menopause status is recommended alongside bisphosphonate therapy (all the bisphosphonate intervention trials have occurred in vitamin D- and calcium-replete patients).
- Oral bisphosphonates should not be taken together with other medications, particularly calcium, because they may affect bisphosphonate absorption. Calcium supplements should not be taken for at least 60 minutes after oral bisphosphonates.
- Low serum vitamin D levels should be corrected to a serum concentration >50 nmol/L before commencing bisphosphonate therapy because low vitamin D levels increase the risk of hypocalcaemia, especially with parenteral bisphosphonates such as zoledronate.
- IV zoledronate needs to be administered over at least 30 minutes because higher infusion rates can increase the risk of renal damage. Zoledronate acid is contraindicated in patients with a calculated creatinine clearance below 35 mL per minute.
- The flu-like side effects from IV zoledronate tend to improve with subsequent infusions.
- The combined use of bisphosphonates with other antiresorptive (eg raloxifene, hormone therapy) or anabolic (teriparatide) drugs is not recommended.
- Good dental hygiene and care is recommended, particularly in those using long-term oral bisphosphonates, to reduce the risk of MRONJ (refer to **Section 5.3**).

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Denosumab

Denosumab

Recommendations

Recommendation 24	Grade
Denosumab is recommended for the treatment of osteoporosis in postmenopausal women at high risk of minimal trauma fracture.	A
Recommendation 25	**Grade**
Denosumab should be considered as an alternative to bisphosphonates for the treatment of men at increased risk of minimal trauma fracture.	B
Recommendation 26	**Grade**
Denosumab therapy should not be interrupted. If denosumab therapy needs to be ceased, patients should be transitioned to bisphosphonate therapy for a minimum of 12 months.	C

Denosumab is a fully human, high-specificity and high-affinity monoclonal antibody against receptor activator of nuclear factor kappa B ligand (RANKL), an important regulator of osteoclast development and activity. Denosumab prevents RANKL binding to its receptor (RANK) on the osteoclast surface. Consequently, osteoclast formation, function, and survival are disrupted, resulting in decreased bone resorption and increased mass and strength of both cortical and trabecular bone. Denosumab significantly reduces the risk of vertebral, non-vertebral, and hip fractures in postmenopausal women.[1–4] Trials in men with low BMD demonstrated similarly significant gains in BMD (8.0% lumbar spine, 3.4% total hip) after two years of denosumab treatment.[5,6]

One RCT showed a decreased incidence of new vertebral fractures in men being treated with ADT for prostate cancer.[7] A meta-analysis of published RCTs found denosumab improved BMD more than bisphosphonate treatment at the lumbar spine, total hip, and FN.[8] This is due to a combination of guaranteed bioavailability from parenteral administration and denosumab's potent antiresorptive effect.

Denosumab has been registered for the treatment of osteoporosis in Australia since 2010 and is subsidised by the PBS for men and women aged >70 years with a T-score of −2.5 or less, and for men and women with a minimal trauma fracture. Denosumab is given as a subcutaneous injection of 60 mg every six months.

Side effects and potential harms

Denosumab used for the treatment of osteoporosis is generally well tolerated. The subcutaneous mode of administration avoids the gastrointestinal side effects associated with oral bisphosphonates and ensures excellent bioavailability. RCT data indicate no significant increase in adverse events with long-term denosumab treatment, including infection, malignancy, pancreatitis, cardiovascular disease, peripheral vascular disease, MRONJ and AFFs.[2,3] Cellulitis has been more frequently reported with denosumab compared with placebo, although the incidence remains low (<0.2 events per 100 subject-years for long-term denosumab).[1] Hypocalcaemia following denosumab administration is a significant risk in patients with severe renal impairment (chronic kidney disease Stage 4 or 5) or in patients receiving dialysis.

The development of multiple vertebral fractures following discontinuation of denosumab therapy due to rebound bone resorption is now well recognised,[9] especially in those with previous vertebral fractures.[10] In the 1001 participants who discontinued denosumab during the FREEDOM study or its extension, the vertebral fracture rate increased from 1.2 per 100 participant-years during the on-treatment period to 7.1 per 100 participant-years following denosumab cessation.[10] The odds of developing multiple vertebral fractures after stopping denosumab were 3.9 (95% CI: 2.1–7.2)-fold higher in those with than without prior vertebral fractures.[10] The mechanism for this remains uncertain, but may be due to a pool of osteoclasts that are activated following loss of the inhibitory effect of denosumab.[11]

A delay in denosumab administration of more than six months was associated with increased risk of rebound fracture.[12] Although definitive measures to minimise the risk of rebound vertebral fractures remain unclear at the time of writing, denosumab should either be continued long-term or cessation should be followed by another antiresorptive medication (i.e., 12 months of oral bisphosphonate or one or more infusions of zoledronate).[13,14]

Evidence Statement

The first randomised placebo-controlled trial of denosumab with fracture as a primary outcome was the FREEDOM trial, published in 2009.[1] In that trial, 7668 women aged 60–90 years with a DXA T-score at the hip or spine of −2.5 to −4.0 were randomised to either 60 mg denosumab or placebo subcutaneously every six months for 36 months. Relative to placebo, denosumab reduced the risk of new radiographic vertebral fractures by 68% (cumulative incidence in treatment and placebo groups 2.3% and 7.2%, respectively; RR 0.32; 95% CI 0.26–0.41; *P*<0.001), hip fractures by 40% (cumulative incidence in treatment and placebo groups 0.7% and 1.2%, respectively; HR 0.60; 95% CI: 0.37–0.97; *P*=0.04) and non-vertebral, non-hip fractures by 20% (cumulative incidence in treatment and placebo groups 6.5% and 8.0%, respectively; HR 0.80; 95% CI: 0.67–0.95; *P*=0.01).[1] The FREEDOM trial was extended for a further seven years (total trial length 10 years), and outcomes of the first two,[2] three,[3] four, and five[4] years of the extension have been reported. The FREEDOM extension used a crossover design. Women who completed three years of denosumab treatment in the original trial were eligible to continue denosumab treatment, whereas those in the placebo group 'crossed over' to receive denosumab for the duration of the extension. After five years of the extension (1542 long-term subjects completing eight years of denosumab treatment and 1462 subjects crossing over to receive five years of denosumab treatment), the respective annual incidence of new vertebral fractures in long-term subjects was 1.5%, 1.3% and 1.3% during extension years 4–5, 6 and 7–8 and the respective annual incidence in crossover subjects was 0.9%, 1.6% and 1.8%.[4] The annual incidence of non-vertebral fractures also remained low in both the long-term and crossover groups during the extension years, varying between 0.7% and 1.8%, and 1.2% and 2.6%, respectively. The cumulative incidence of hip fractures over the five-year extension was 0.7% in the long-term group and 1.1% in the crossover group (mean age 79 years at year 8 of extension).[4]

The two-year Denosumab Fracture Intervention Randomised Placebo Controlled Trial (DIRECT)[15] measured fracture incidence with denosumab treatment versus placebo in Japanese men and women aged >50 years with 1–4 prevalent fractures and mean DXA T-scores of −2.8 at the lumbar spine and −2.0 at the hip. Over 24 months, the incidence of new or worsening vertebral fracture was 3.6% in the denosumab group, compared with 10.3% in the placebo group, a risk reduction of 65.7% (*P*=0.0001). Subgroup analysis of female subjects showed that the risk of new or worsening vertebral fracture at 24 months was reduced by 63.2% in the denosumab compared with placebo group (HR 0.37; 95% CI: 0.21–0.65; *P*=0.0004). The incidence of new vertebral fracture was reduced by 74% (*P*<0.0001). Subgroup analysis of male subjects showed a new or worsening vertebral fracture incidence at 24 months of 0% in denosumab-treated men, compared with 12.5% in men treated with placebo. However, this difference did not reach statistical significance (*P*=0.07) due to the small sample size (23 men in the denosumab arm and 24 in the placebo arm).[15] A one-year crossover extension (n=775) of the DIRECT trial showed

maintenance of low-fracture rates, with no difference in annualised fracture incidence between two and three years of treatment in the long-term group.[16] As expected, the incidence of new and worsening vertebral fractures was reduced in the crossover group after commencement of denosumab treatment; the RaRs comparing years 2 and 1 and years 3 and 1 were 2.87 (*P*=0.003) and 0.23 (*P*=0.0003), respectively.[16] These results suggested that the magnitude of effect on fracture risk reduction by denosumab depended on treatment duration. Overall, in men with low BMD treated with denosumab, increases in BMD were similar to those seen in postmenopausal women.[5]

Safety

The original three-year FREEDOM trial showed no significant increase in the incidence of cancer or infection compared with placebo.[1] There was no increase in serious adverse events, including coronary heart disease and stroke, compared with placebo, but a significant increase in cellulitis requiring hospitalisation was reported (0.3% in the denosumab group compared with <0.1% in the placebo group; *P*=0.002). No cases of MRONJ or AFFs were reported. In the five-year extension study, adverse events for the duration of the FREEDOM extension, including cellulitis and other serious infection, were similar to those in the denosumab group in the original FREEDOM trial, with no increases over time.[3] A total of two cases of AFF occurred in year 3 (in the crossover group) and year 7 (long-term group) of denosumab treatment, and a total of eight cases of MRONJ occurred in years 2 and 4 (in the crossover group) and years 6 and 7 (long-term group) of denosumab treatment. The cumulative incidence rates during the FREEDOM extension were 4.2 per 10,000 subject-years for MRONJ and 1.0 per 10,000 subject-years for AFF.[4] Adverse event rates were similarly low in the two-year DIRECT trial and one-year DIRECT extension, with no significant difference between treatment and placebo groups.[15,16] One case of MRONJ occurred during the extension in a crossover subject (one year of denosumab treatment).[15,16] Although no head-to-head trials have been published, a systematic review of nine RCTs (n=4890) comparing the safety and efficacy of denosumab with bisphosphonate treatment for up to two years found no statistically significant difference between groups in terms of fracture risk or adverse events.[17]

Definitive measures to minimise the risk of rebound vertebral fractures remain unclear at the time of writing. To avoid this phenomenon, denosumab could be continued long term. However, if denosumab cessation is required, an observational study suggested that after 2–5 years of denosumab, 5 mg IV zoledronate administered six months following the last denosumab injection protected against the occurrence of multiple vertebral fractures.[13] Zoledronate also appeared to retain 66% of the BMD gained with denosumab at the lumbar spine and 49% at the total hip.[13] However, a recent randomised open-label study found that IV zoledronate did not fully prevent the increased bone turnover and bone loss

observed following denosumab cessation, even when IV zoledronate was readministered following a rise in bone turnover markers or a fall in BMD.[14] More evidence is required to guide therapy in this area.

Practical tips and precautions

- Hypocalcaemia is an identified risk of denosumab treatment, particularly in patients with severe renal impairment (creatinine clearance <30 mL per minute or receiving dialysis). Hypocalcaemia must be corrected prior to treatment initiation, and calcium levels monitored during treatment of such high-risk patients, especially in the first two weeks of initiating therapy.
- Dietary calcium intake and serum 25(OH)D levels should be optimised, using supplements if required, prior to commencing denosumab therapy.
- Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.
- Unlike bisphosphonates, which are sequestered in bone, the effects of denosumab on bone resorption do not persist after treatment has stopped. Therefore, regular six-monthly administration is required for continued reduction of fracture risk.
- Strict six-monthly dosing of denosumab is important to minimise the risk of rebound vertebral fractures.
- Cessation of denosumab should be followed by antiresorptive therapy. Specialist review may be required, particularly in patients with high fracture risk.

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Romosozumab

Romosozumab

Recommendations

Note: In Australia, romosozumab was only listed on the PBS in April 2021 and so these recommendations are based on current limited evidence.

Recommendation 27	Grade
Romosozumab is recommended as first-line therapy for the treatment of osteoporosis in postmenopausal women at very high risk of minimal trauma fracture.	A
Recommendation 28	**Grade**
Romosozumab is recommended as first-line therapy for the treatment of osteoporosis in men at very high risk of minimal trauma fracture.	C

Like denosumab, romosozumab is a 'targeted therapy' for the treatment of osteoporosis and is the most recent pharmacological therapeutic addition. Romosozumab, a monoclonal antibody, is a potent bone anabolic agent (builds bone) that specifically targets and binds sclerostin. Unlike bisphosphonates and denosumab, which predominantly reduce bone resorption, and teriparatide, which predominantly increases bone formation, romosozumab both increases bone formation and reduces bone resorption. This unique mechanism of action leads to a marked increase in BMD, greater than what is seen with oral alendronate or teriparatide.[1,2]

Romosozumab is administered as a subcutaneous injection (two 105-mg syringes) once a month. Two injections are given at the same time once a month for 12 months. Romosozumab has been shown to reduce vertebral and non-vertebral fractures in postmenopausal women with osteoporosis at high risk of fracture.[3,4] Romosozumab has also been shown to reduce vertebral, non-vertebral, and hip fractures compared with the antiresorptive drug, alendronate. In a post hoc analysis of the FRActure study in postmenopausal woMen with ostEoporosis (FRAME), romosozumab had greater efficacy in reducing vertebral fractures than denosumab.[3,4] These studies, and those of teriparatide compared with

risedronate, indicate that bone anabolic agents are superior to antiresorptive drugs in reducing vertebral and clinical fractures.[1–4] Although fracture reduction data in men are lacking, romosozumab was effective in increasing BMD and appeared safe in men with osteoporosis.[5]

Evidence Statement

In postmenopausal women

FRAME, an RCT of 7180 postmenopausal women with DXA T-scores of −2.5 to −3.5 at the total hip or FN, randomised participants to subcutaneous romosozumab 210 mg or placebo monthly for 12 months.[3] Thereafter, patients received denosumab at the usual dose of 60 mg subcutaneously every six months for 12 months. At 12 months, new vertebral fractures had occurred in 16 of 3321 patients (0.5%) in the romosozumab group, compared with 59 of 3322 patients (1.8%) in the placebo group, a 73% lower risk with romosozumab (P<0.001). Clinical fractures occurred in 58 of 3589 patients (1.6%) in the romosozumab group, compared with 90 of 3591 patients (2.5%) in the placebo group, a 36% lower risk with romosozumab (P=0.008). Non-vertebral fractures occurred in 56 of 3589 patients (1.6%) in the romosozumab group and in 75 of 3591 (2.1%) in the placebo group (P=0.10). At 24 months, rates of vertebral fractures were significantly lower in the romosozumab than placebo group following transition to denosumab (0.6% [21/3325] versus 2.5% [84/3327] in the romosozumab and placebo groups, respectively; a 75% lower risk with romosozumab; P<0.001). Adverse events were balanced between groups. In postmenopausal women with osteoporosis, romosozumab was associated with a lower risk of vertebral fracture than placebo at 12 months and, after the transition to denosumab, at 24 months.[3]

The superior efficacy of romosozumab compared with an antiresorptive agent (alendronate) in patients at high risk of fracture was shown in the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) of 4093 postmenopausal women with osteoporosis and prevalent vertebral fractures.[4] Participants were randomised to either romosozumab 210 mg monthly or alendronate 70 mg weekly for one year, followed by open-label treatment with alendronate for up to two years. Compared with alendronate, romosozumab increased BMD by approximately 2.5-fold at the spine and twofold at the hip in year 1, and vertebral fracture relative risk was 37% and 48% lower at year 1 and 2, respectively, compared with standard-of-care alendronate. At study completion (median exposure 33 months), relative risk reductions of 27% for clinical fractures, 19% for non-vertebral fractures and 38% for hip fractures were seen for the group initially treated with romosozumab relative to the group treated with alendronate alone.[4] In postmenopausal women with osteoporosis at high risk of fracture, romosozumab treatment for 12 months followed by alendronate significantly reduced new vertebral, clinical and non-vertebral fractures compared with alendronate.

An unexpected imbalance in adjudicated serious cardiovascular adverse events was observed in ARCH, with 50 (2.5%) patients in the romosozumab group and 38 (1.9%) in the alendronate group reporting these events (OR 1.31; 95% CI: 0.85–2.00).[4] This was not

observed in the larger FRAME study, which enrolled slightly younger patients with less severe osteoporosis.[3] The mechanisms and implications for this observation remain uncertain, with the possibility of a cardioprotective effect of alendronate raised.

Romosozumab was compared to the other anabolic bone agent, teriparatide, in the STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture previously treated with bisphosphonatE therapy (STRUCTURE).[1] Subjects with prior bisphosphonate therapy and a DXA T-score ≤−2.5 at the total hip, lumbar spine or FN and a history of non-vertebral fracture after the age of 50 years or vertebral fracture were randomised to either subcutaneous romosozumab 210 mg once monthly (n=218) or subcutaneous teriparatide at the standard dose of 20 mcg once daily (n=218). There was significantly greater mean percentage change from baseline in favour of romosozumab at the total hip at month 12 compared with teriparatide (2.6% versus −0.6%, respectively; *P*<0.0001), for a mean difference between the two groups of 3.2% (*P*<0.0001).[1] The relatively small increment in BMD even with romosozumab may have been due to 'blunting' of bone anabolism from prior bisphosphonate use. Although the study was too small to look at fracture outcomes, in postmenopausal women with osteoporosis at high risk of fracture previously treated with bisphosphonate therapy, 12 months of romosozumab resulted in statistically significant increases in BMD at the total hip, femoral neck and lumbar spine compared with teriparatide.

In men

Romosozumab was studied in men with osteoporosis in the placeBo-contRolled study evaluatIng the efficacy anD safety of romosozumab in treatinG mEn with osteoporosis (BRIDGE), which included men (n=245) aged 55–90 years with a DXA T-score at the lumbar spine, total hip, or FN of ≤−2.5, or ≤−1.5 with a history of fragility fracture.[5] Patients were randomised to either romosozumab 210 mg (n=163) or placebo (n=82) subcutaneously once a month for 12 months.[5]

After 12 months, a significantly greater mean increase from baseline in lumbar spine BMD was seen in those on romosozumab compared with placebo (12.1% vs 1.2%; *P*<0.001). Lesser, but still significant, BMD increments were seen at the total hip and FN with romosozumab.[5] Romosozumab appeared effective and safe in men with osteoporosis. There are no intervention studies evaluating fracture outcomes in men.

Practical tips and precautions

- Monthly romosozumab subcutaneous injection is more convenient than the daily subcutaneous injections of the other bone anabolic agent (teriparatide).
- The absolute risk reduction with romosozumab over bisphosphonate treatment is in the order

of 1–1.3% fewer fractures per year.

- A possible increase in cardiovascular risk with romosozumab[4] means it should be avoided in those with a history of myocardial infarction or stroke. More data are needed to guide clinical practice in this area. At the time of writing (7 December 2023), the Therapeutic Goods Administration (TGA) had posted a safety update on their website about this (https://www.tga.gov.au/news/safety-updates/new-warnings-romosozumab-evenity-cardiovascular-risks (https://www.tga.gov.au/news/safety-updates/new-warnings-romosozumab-evenity-cardiovascular-risks)).
- Although current PBS criteria to access romosozumab are identical to those for teriparatide and limit the use of romosozumab to individuals with severe osteoporosis (T-score ≤–3.0) who have sustained fractures despite an antiresorptive therapy, increasing evidence suggests romosozumab is best used as initial therapy in those with severe osteoporosis for its potent anabolic effect, followed by an antiresorptive (ie sequential) therapy.[1,4,6] (As of 1 February 2023, the PBS mandates romosozumab needs to be initiated by a consultant physician.)

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Menopausal Hormonal Therapy

Menopausal Hormonal Therapy

Recommendations

Recommendation 29	Grade
Consider oestrogen replacement therapy to reduce the risk of fragility fractures in postmenopausal women within 10 years of menopause. The increased risk of adverse events associated with treatment should be carefully weighed against benefits.	A
Recommendation 30	**Grade**
Selective oestrogen receptor modulators (SERMs) should be considered as a treatment option for postmenopausal women with osteoporosis where vertebral fractures are the major osteoporosis risk (based on low spine BMD and/or an existing vertebral fracture) and where other agents are poorly tolerated. SERMs may be particularly useful in younger postmenopausal women at risk of vertebral fracture with a prior or family history of breast cancer.	A

Oestrogen

Oestrogen acts to decrease bone resorption and promote bone formation. Oestrogen replacement therapy effectively prevents loss of BMD and reduces the risk of fractures when given at, or near, menopause. Oestrogen therapy is most appropriate in women with vasomotor symptoms of menopause who are at risk of osteoporosis.[1–5] Menopausal hormonal therapy (MHT) has been shown to reduce fracture risk regardless of falls or baseline FRAX®.[6] Postmenopausal women at high risk of fracture may be more appropriately prescribed bone-specific antiresorptive or osteoanabolic therapies. Where appropriate, concurrent MHT and bone-specific therapies can be considered.

The minimum effective dose of oestrogen therapy on bone loss has yet to be clearly established,[5] but beneficial effects of oestrogen therapy can be achieved by oral or transdermal administration, including patches and gels. The choice of oestrogen will also depend on patient preference and tolerance of side effects, including local skin irritation to transdermal formulations or migraines with oral oestrogens. Breast tenderness, swelling, and vaginal spotting are frequent side effects of oestrogen therapy, and a lower-dose regimen should be commenced with close assessment of tolerance. Lower doses of oestrogen may also be effective in preventing postmenopausal bone loss. However, higher doses may be considered in patients who demonstrate ongoing bone loss with low-dose oestrogen replacement, with attention paid to calcium intake and vitamin D status, provided the risk associated with oestrogen replacement therapy is not increased (e.g., clotting, cardiovascular disease, or breast cancer). Women with a history of oophorectomy may require a higher-dose oestrogen regimen at an earlier time point.

Ideally, oestrogen therapy should be given continuously (i.e., without a break in therapy) and a transdermal approach is ideal to avoid a greater risk of thrombosis in women taking oral oestrogen preparations. Women at higher risk of thrombosis, such as those with previous venous thrombosis, Factor V Leiden mutations, or other coagulopathy, should not be prescribed oral oestrogens.

Adjuvant progestogens are necessary in women who still have a uterus to protect against endometrial cancer. Progestogens may be given cyclically for 10–14 days each month in perimenopausal women or as continuous therapy combined with oestrogen in postmenopausal women. The latter is more suitable for women more than two years postmenopause to avoid the initial irregular bleeding commonly seen with this regimen being unduly prolonged.

Tibolone

Tibolone is a form of MHT with oestrogenic, progestogenic, and androgenic effects and does not need to be given with a progestogen. It has similar efficacy to traditional MHT in reducing fracture risk and is used for the relief of vasomotor menopausal symptoms. Tibolone, at a dose of 1.25 mg daily, reduces the risk of fractures in postmenopausal women. However, its use in older postmenopausal women should be undertaken with caution due to a higher risk of stroke.[3] Currently, tibolone is not subsidised by the PBS.

All postmenopausal women on MHT should have regular mammographic screening and frequent assessment of risks and benefits of continuing therapy beyond five years of postmenopause. Upon ceasing MHT, bone density is likely to decline because the effects of oestrogen on bone are reversible. A long-term treatment approach to treat osteoporosis may then be required following MHT.

Selective estrogen receptor modulators

Available on the PBS for treatment of postmenopausal osteoporosis, SERMs such as raloxifene have evidence for breast cancer prevention,[7] so their use can be tailored to suit an individual's unique risk factor profile and they may be particularly useful in the younger postmenopausal female with low spine BMD and a prior or family history of breast cancer.

Although there is excellent evidence for raloxifene in the reduction of vertebral fracture risk, there is minimal evidence for reduction in non-vertebral fractures.[8] Therapy should be continuous; there is no need for concomitant progestogens and, following therapy, a long-term treatment approach to osteoporosis is required because the effects on bone density are reversible. Raloxifene has also been associated with an increase in hot flushes and thromboembolism.[7,8]

Side effects and potential harms

Treatment effect

The role of long-term MHT in the prevention and management of osteoporosis remains controversial, following results of the Women's Health Initiative (WHI) study of combined oestrogen and progestin therapy[4] and its study of oestrogen-alone therapy.[2]

Tibolone has a different side effect profile from traditional MHT. A Cochrane systematic review found no evidence for an increase in breast cancer in women with no history of breast cancer (OR 0.52; 95% CI: 0.21–1.25).[9] However, tibolone does appear to increase breast cancer recurrence in those with treated breast cancer.[9,10] There is no evidence for increased heart disease or thromboembolic events with tibolone, but in older women there was an increased risk of stroke.[3]

Raloxifene may increase hot flushes and is likely to aggravate vasomotor symptoms. Like traditional MHT, raloxifene is associated with increased thromboembolic events, but has not been associated with heart disease or overall risk of stroke.[11] In one study of women at high heart disease risk, raloxifene increased fatal, but not overall, stroke risk.[7]

Evidence Statement

Treatment effect

In a clinical trial of 7705 women randomised to two doses of raloxifene or placebo followed for up to four years, there was a reduction in vertebral fractures (RR 0.64; 95% CI: 0.53–0.76) at the approved dose of 60 mg per day.[8] There was no significant reduction in non-vertebral fractures (RR 0.93; 95% CI: 0.81–1.06). Similar results were found for another good-quality study of raloxifene in over 10,000 women at high risk of heart disease at baseline.[7]

There is good evidence that, compared with placebo, oestrogen is associated with a decreased risk of vertebral, non-vertebral, and hip fractures. This effect was observed in the analysis for all postmenopausal women (OR not reported), as well as for groups at higher risk of fractures (RR ~0.7).[1] In two clinical trials conducted by the WHI, conjugated oestrogen in combination with progestin in postmenopausal women (n=16,608) or conjugated equine oestrogen (CEE) alone in women after hysterectomy (n=10,739) were shown to reduce the risk of osteoporotic fractures.[2,4] Participants taking CEE 0.625 mg and medroxyprogesterone acetate 2.5 mg per day in a combined tablet (as opposed to oestrogen therapy) for an average of five years had significant reductions in total fractures (HR 0.76; 95% CI: 0.69–0.85; *P*=0.05) and hip fractures (HR 0.66; 95% CI: 0.45–0.98; *P*=0.05).[4] Participants taking CEE 0.625 mg per day for an average of six years had significant reductions in the rates of all osteoporotic fractures (HR 0.70; 95% CI: 0.63–0.79; *P*=0.01) and hip fractures (HR 0.61; 95% CI: 0.41–0.91; *P*=0.01).[3] An RCT of tibolone in 4500 women over three years found decreased risks of vertebral fracture (HR 0.55; 95% CI: 0.41–0.74) and non-vertebral fracture (HR 0.74; 95% CI: 0.58–0.93).[3]

Safety

Oestrogen alone or combined with progestagens

The WHI reported that in the oestrogen-alone group there was no increased risk of invasive breast cancer or cardiovascular disease, although the other outcomes were similar to the combined group.[2] For the combined oestrogen/progesterone group, increased risk of invasive breast cancer has been reported in multiple analyses, although the initial report of increased coronary heart disease was no longer significant in subsequent analyses.[2–5,9] Increased risks of thromboembolic events and stroke are reported for both groups. Subsequent to the initial publication, there have been multiple reanalyses of the data, including by age of initiation of MHT. The side effect profile is more favourable for those women starting MHT within 10 years of menopause (age 50–59 years) with low absolute risks of thromboembolic events and stroke.[9]

In a large meta-analysis[12] and nested case-control study,[13] the risk of breast cancer increased steadily with longer duration of MHT use and was greater in those on combined oestrogen/progesterone therapy compared with oestrogen alone, with the increased risk persisting for several years following cessation.[12] Different progesterones are associated with differential breast cancer risk, with micronised progesterone having the lowest risk.[14]

Long-term follow-up (median follow-up >20 years) of the WHI study cohort found that CEE alone compared with placebo in women with hysterectomy was associated with lower breast cancer incidence (HR 0.78; 95% CI: 0.65–0.93) and lower breast cancer mortality (HR 0.60; 95% CI: 0.37–0.97).[15] However, compared with placebo, CEE plus medroxyprogesterone acetate in women with a uterus was associated with higher breast cancer incidence (HR 1.28; 95% CI: 1.13–1.45), but no difference in breast cancer mortality (HR 1.35; 95% CI: 0.94–1.95).[15]

The most recent systematic review that looked at 27 RCTs and 47 observational studies between 2009 and 2019 reported an increased risk of thromboembolic events (for RCTs, summary estimate [SE] 1.70 [95% CI: 1.33–2.16]; for observational studies, SE 1.32 [95% CI: 1.13–1.54]).[16] The authors noted that the study populations in the RCTs were older and had more underlying disease than those in the observational studies. In the same systematic review, an increased stroke risk was only seen in the RCTs (SE 1.14; 95% CI: 1.04–1.25) and a decreased risk of myocardial infarction was seen in observational studies (SE 0.79; 95% CI: 0.75–0.84).[16] Multiple subgroup analyses were also performed to better understand the clinical effects of MHT. These analyses suggest that choice of MHT, underlying disease, and timing of initiation should be considered. In subgroup analyses of observational studies, a decreased risk of all-cause death was observed among oestrogen-only MHT (SE 0.85; 95% CI: 0.77–0.95) and early users after menopause (SE 0.68; 95% CI: 0.51–0.92).[16] In addition, increased risk of stroke was seen in observational studies in women administered oral MHT (SE 1.24; 95% CI: 1.11–1.39), whereas a decreased risk of stroke was observed in women administered non-oral MHT (SE 0.86; 95% CI: 0.77–0.96). Overall, analyses favour earlier initiation (within 10 years of menopause) and non-oral MHT, and support safe use for at least five years in healthy women initiating treatment before the age of 60 years. The International Menopause Society supports tailoring MHT duration to the individual's needs.[17]

Tibolone

An RCT of women aged >60 years reported a reduction in the risk of invasive breast cancer (absolute risk reduction [ARR] 1.9 per 1000 person-years; 95% CI: 0.5–3.4; *P*=0.02) and colon cancer (ARR 1.3 per 1000 person-years; 95% CI: 0.1–2.6; *P*=0.04) associated with tibolone therapy.[3] However, the relative hazard for stroke was 2.19 (95% CI: 1.14–4.23) and the absolute risk increase was 2.3 per 1000 person-years (95% CI: 0.4–4.2), leading to early cessation of the trial. Absolute risk increased more in participants aged >70 years (absolute risk increase 3.1 per 1000 person-years). There was

no increased risk of heart disease or venous thromboembolic events.[3] In a subsequent study of women already treated for breast cancer, tibolone was found to decrease vasomotor symptoms and maintain BMD, but there was an increased risk of breast cancer recurrence (HR 1.40; 95% CI: 1.14–1.70).[10] Similar to the earlier study, there was no increased risk of venous thromboembolic events or heart disease in this younger group.

Raloxifene

In the four-year follow-up of the pivotal raloxifene Multiple Outcomes of Raloxifene Evaluation (MORE) study,[8,18] there was an increased risk of thromboembolic events, with an RR of 2.76 (95% CI: 1.30–5.86) for deep venous thrombosis and 2.76 (95% CI: 0.95–8.01) for pulmonary embolism. Unlike MHT, there was a reduced risk of breast cancer (RR 0.38; 95% CI: 0.24–0.58) and no increased risk of cardiovascular events.[19] In a subsequent RCT of raloxifene in over 10,000 women with either established heart disease or risk factors for heart disease, there was a similar reduction in breast cancer (primarily estrogen receptor positive) and no increased risk of primary coronary events, overall risk of stroke or overall deaths.[7] However, there was an increased risk of fatal strokes (HR 1.49; 95% CI: 1.00–2.24) and venous thromboembolism (HR 1.44; 95% CI: 1.06–1.95).[7]

Practical tips and precautions

- GPs should discuss with patients the long-term risks and benefits of MHT, especially breast cancer and thromboembolic and cardiovascular effects. Side effects of traditional MHT are minimised, with absolute risk low, if given within 10 years of menopause.
- The side effect profiles of traditional MHT, tibolone and raloxifene are different. MHT is ideal for postmenopausal women with vasomotor menopausal symptoms and who are at risk of osteoporosis, in the absence of contraindications.
- Women taking MHT should have at least an annual consultation with their GP to review their risks and the ongoing need for MHT.
- Individuals who require immobilisation for any period (eg hospitalisation or a long plane trip) should cease MHT or raloxifene for a week before and after.
- Postmenopausal women taking MHT should maintain adequate calcium intake (from dietary sources or supplements) and be vitamin D replete.
- Raloxifene should not be used in combination with oestrogen therapy.
- The use of bone-specific antiresorptive or anabolic therapies is more appropriate than MHT in patients at high risk of fracture.
- The risks of MHT must be weighed against the clear benefits of MHT in women with menopausal vasomotor symptoms and osteoporosis, in particular the beneficial effects on quality of life and fracture prevention.

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Recombinant human parathyroid hormone

Recombinant human parathyroid hormone

Recommendations

Recommendation 31	Grade
Recombinant human parathyroid hormone (teriparatide) treatment is recommended to reduce fracture risk in postmenopausal women with osteoporosis who have sustained a subsequent fracture while on antiresorptive therapy, or in those at very high fracture risk.	A
Recommendation 32	**Grade**
Recombinant human parathyroid hormone (teriparatide) treatment is recommended to reduce fracture risk in men aged over 50 years with osteoporosis who have sustained a subsequent fracture while on antiresorptive therapy, or in those at very high fracture risk.	C

Recombinant human parathyroid hormone (PTH) is approved in Australia in the form of hPTH(1–34), also known as teriparatide. Teriparatide acts predominantly on osteoblasts to increase new bone formation on trabecular and cortical surfaces by preferentially stimulating osteoblastic bone formation over osteoclastic bone resorption. Teriparatide acts to increase osteoblast lifespan by reducing osteoblast apoptosis (cell death) and inducing the recruitment and formation of new osteoblasts – the cells that make new bone. The bone-remodelling rate and the amount of bone deposited in each remodelling cycle is increased. Cancellous bone connectivity, trabecular thickness and cortical width are increased, as is periosteal bone formation, which is responsible for increasing cortical width and producing an increase in bone size. Skeletal mass and bone strength are also increased.[1]

Teriparatide increases lumbar spine and FN BMD and decreases vertebral and non-vertebral fractures in postmenopausal osteoporosis with prior fracture. Hip fracture risk has not been assessed.[2] Teriparatide has also been shown to improve new, worsening and moderate-to-severe back pain and

reduce height loss in patients who have sustained one or more new vertebral fractures.[3] Teriparatide increases BMD at the lumbar spine and FN in men with osteoporosis, but there are no data on fracture reduction in this population.[4,5]

Teriparatide has been studied at a maximum continuous course of 24 months with beneficial effects on bone density and fracture risk. It is PBS subsidised for 18 months per lifetime per individual (TGA approved for 24 months) for patients with severe osteoporosis and a very high risk of fracture who have:

- a BMD T-score of ≤−3.0
- had two or more fractures due to minimal trauma
- experienced at least one symptomatic new fracture after at least 12 months continuous therapy with an antiresorptive agent (eg bisphosphonate or denosumab).

Side effects and potential harms

Dizziness, leg cramps, nausea, injection reactions and headache are the most common side effects, occurring in up to 5% of patients. These are generally mild and do not require treatment discontinuation. Because transient hypercalcaemia has been noted, checking serum calcium shortly after treatment is recommended.[2] Mild increases in uric acid without the development of acute gout and small increases in urinary calcium excretion without nephrolithiasis have been reported.[6] Oncogenicity studies in rats treated with high doses of teriparatide for near-lifetime duration revealed an increased risk of osteogenic sarcoma.[7] However, surveillance of human osteosarcoma cases has found no relationship with teriparatide.[8]

Evidence Statement

Treatment of osteoporosis in postmenopausal women

A systematic review reported 10 moderate- and good-quality RCTs (including seven double-blind RCTs) investigating the effectiveness of hPTH(1–34).[2] One trial[3] in that systematic review reported fracture risk as a primary outcome measure. The trial compared hPTH(1–34) to calcium in postmenopausal women, reporting a reduction in the risk of new vertebral fractures for hPTH(1–34) 20 mcg per day (RR 0.35; 95% CI: 0.22–0.55). The ARR for vertebral fractures was 9% and the ARR for non-vertebral fractures was 3% (RR 0.47; 95% CI: 0.25–0.88) for hPTH(1–34) 20 mcg per day.[3] Six moderate-to-good quality RCTs reported in the systematic review compared PTH to placebo or an active comparator and reported BMD as an outcome measure.[2] The duration of the trials was 1–3 years. Participants treated with hPTH(1–34) 20 mcg per day had significant increases in lumbar spine BMD of 9.7–10.3% and increases in FN BMD of 2.8–3.9%.

Treatment of osteoporosis in men

In a good-quality trial, men with idiopathic osteoporosis (n=23) were randomly assigned to hPTH(1–34) 25 mcg versus placebo.[4] After 18 months, BMD increased significantly by 13.5% and 2.9% at the lumbar spine and FN, respectively. Total hip BMD did not change significantly, but there was a significant decrease of 1.2% at the distal radius.[4] Another good-quality trial was conducted in men with low BMD who were predominantly hypogonadal (n=437).[5] Participants were treated with 20 or 40 mcg hPTH(1–34) versus placebo with calcium and vitamin D. After 12 months, lumbar spine BMD increased by 5.4% with 20 mcg hPTH(1–34), compared with no change with placebo. There was no significant difference in fracture rate between hPTH(1–34) and placebo.[5]

Combination with antiresorptive therapies in postmenopausal osteoporosis

There is strong evidence that combination therapy with alendronate and teriparatide may blunt the anabolic effect of teriparatide on BMD.[2] There are no fracture data comparing the effect of combination teriparatide and alendronate with that of teriparatide alone.[2] An open-label RCT has compared the effect on BMD between teriparatide and denosumab alone, or in combination.[9] At 24 months, combination treatment increased BMD at the lumbar spine and hip more than either treatment alone; the study was not powered to detect an effect on fracture rate.[9]

Safety

An increased risk of osteosarcoma was reported in a lifelong carcinogenicity study involving Fischer rats given high-dose hPTH(1–34) from infancy through senescence (from eight weeks to two years of age).[7] Osteosarcoma was found with all doses and, in

the lower dose ranges, was first detected after about 20 months of therapy. There have been no reports of osteosarcoma in clinical trial subjects and, conversely, after seven years of the Osteosarcoma Surveillance Study (an ongoing 15-year surveillance study initiated in 2003), there have been no osteosarcoma patients who have reported prior exposure to teriparatide.[8] Nine trials investigating hPTH(1–34) reported post-dose hypercalcaemia (serum calcium >2.6 mmol/L) that ranged from 3% to 11% among patients taking hPTH(1–34) 20 mcg, compared with 0–3% among those taking the comparator.[2] These episodes were mild, with serum calcium concentrations usually normalising within 24 hours and no clinical sequelae. There were no reported increases in renal stones. hPTH(1–34) 20 mcg was associated with a significant increase in patients experiencing dizziness (3%) and leg cramps (range 2–8%).

Practical tips and precautions

- Teriparatide is given as a daily subcutaneous injection via a multidose pen device. (This may be an issue for those with poor hand function or those who are vision-impaired or needle-phobic.)
- Teriparatide is generally restricted to patients at very high risk of fracture. However, the cost has fallen with the recent introduction of a teriparatide biosimilar (Terrosa™).
- Due to possible increased background risk of osteosarcoma, teriparatide is not recommended for patients with Paget's disease, prior skeletal irradiation, bony metastases or prior skeletal malignancies, or for those with metabolic bone diseases (other than osteoporosis) or pre-existing hypercalcaemia.
- BMD decreases within 12 months of stopping teriparatide, unless followed by sequential treatment with an antiresorptive drug.

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Ongoing monitoring

Ongoing monitoring

Recommendations

It is important to distinguish ongoing BMD monitoring for patients on, and not on, treatment.

Recommendation 33	Grade
Regularly reassess fracture risk and the requirement for anti-osteoporotic therapy in patients not receiving therapy, but who remain at increased fracture risk.	C

The frequency of reassessment should be determined by the individual's overall fracture risk or circumstances that may worsen bone loss. Vigilance should be exercised for height loss and new episodes of back pain, which may indicate a new vertebral fracture.

Recommendation 34	Grade
Clinically review all patients 3–6 months after initiating pharmacological therapy for osteoporosis, and 6–12 monthly thereafter for medication side effects and therapy adherence.	C
Recommendation 35	**Grade**
Measurement of bone turnover markers should be confined to specialist practice. Measurement of bone turnover markers may be useful for monitoring medication adherence and efficacy and for evaluation of secondary causes of bone loss.	D

At present, there are no validated criteria for failure of medical therapy. However, therapeutic failure should be considered if:

- minimal trauma fractures occur (usually more than one fracture event), in which case other non-pharmacological measures need to be or reinforced, as required (refer **to Section 2**)
- there is a documented decrease in height ≥3 cm since the last examination or acute back pain, which may be symptomatic of a new fracture; in these cases, a radiological examination is recommended.

Osteoporosis treatment is required for many years. Monitoring patients with BMD assessment by DXA must be at practical intervals to check gradual improvement while avoiding unnecessary imaging. A meta-regression of published trials has shown that greater improvements in BMD were strongly associated with greater reductions in vertebral and hip fracture, but not non-vertebral fractures.[1] It also found that improvement in total hip BMD accounted for 56% of the fracture risk reduction seen with osteoporosis treatment.[1]

Practical tips and precautions

For those ON bone protective pharmacotherapy:

- In patients with confirmed osteoporosis, a repeat BMD test is generally not required, but may be conducted before initiating a change in, or cessation of, anti-osteoporotic therapy.
- The occurrence of a new minimal trauma fracture while on bone-protective pharmacotherapy may warrant a repeat DXA sooner than two years to detect ongoing BMD loss. This may prompt a treatment switch (e.g., to parenteral antiresorptive therapy [denosumab or zoledronate] or an osteoanabolic agent).

For those NOT on bone protective pharmacotherapy:

- A decrease in BMD greater than measurement error is generally not seen before two years; hence, follow-up bone densitometry is not generally recommended at intervals of less than two years.[2,3] Specific exceptions are patients at high risk of bone loss (e.g., those on corticosteroids, ADT or aromatase inhibitors), in whom yearly monitoring may be warranted.
- It may be appropriate to repeat DXA assessment after two years in patients at risk of developing osteoporosis, to assist in re-evaluation of fracture risk (refer also to **Sections 1.2** and **1.3**).
- Consider timing of subsequent BMD measurement based on the current absolute risk and likelihood of change in BMD to an extent that would change management.

General advice

- Wherever possible, perform repeat BMD testing on the same instrument, or at least the same type (manufacturer and model type) of instrument, to improve the comparability of results in interpreting change in BMD. The lumbar spine and total proximal femur are the optimal sites to monitor BMD. Dual-hip DXA should also be considered to improve diagnosis and precision of monitoring at the hip.[4]
- Changes of <5% or 0.05 g/cm^2 at the lumbar spine or hip are within the precision error of most DXA machines and should therefore be regarded as representing no significant change.
- A radiographic assessment should be initiated if new fractures are suspected (eg height loss ≥3 cm, new or acute pain).

- Refer to **Appendix C**, which provides a list of current Medicare Benefit Schedule (MBS) item numbers for bone density testing using DXA.

Biochemical markers of bone turnover

Biochemical markers of bone turnover decrease rapidly (within three months) after initiation of antiresorptive drugs such as oral or IV bisphosphonates, denosumab or raloxifene, and increase with commencement of osteoanabolic therapies.[5–8] They have also been shown to provide information on the antifracture efficacy of these agents.[8,9] For these reasons, bone turnover markers may be used to assess the effect of therapy on bone metabolism.

Measuring a bone resorption marker (e.g., serum C-telopeptide) after three months of antiresorptive treatment and finding a level in the lower half of the premenopausal range generally indicates adherence with antiresorptive therapy. However, in the absence of clear evidence of improved patient outcomes from the use of bone resorption markers, as well as cost-effectiveness data, their routine use in patient monitoring in general practice is not recommended.

Evidence Statement

Failure to observe an increase in BMD during therapy with bisphosphonates, denosumab, or raloxifene does not indicate decreased antifracture efficacy of the drug and is no indication to change treatment.[10–15] A stable or increasing BMD during treatment should be considered as adequate therapy response.[10,12–16] In contrast, detectable loss of BMD while on antiresorptive treatment may be associated with negative clinical outcomes (increased fracture risk) and should prompt review of diagnosis, treatment regimen, and patient medication adherence.[2,17]

A decision to change treatment based solely on a new fracture occurring during treatment is not supported by RCT data. Because fractures will occur in some individuals even on effective therapy, fracture per se is not an indication to change. However, patient tolerance, treatment adherence, and side effect profile may suggest changing the type or route of administration of therapy on an individual basis. Evidence of lack of response (e.g., falling BMD or failure to achieve expected changes in bone turnover markers) could justify a change. However, adherence with, and the correct mode of taking medications should be evaluated first, because problems with these aspects are the most likely explanation. Although long-term adherence with non-pharmacological and pharmacological interventions is crucial, it is often low, even in patients with fractures.[18,19]

Follow-up visits, close contact between patient and health professionals, and repeat BMD and/or bone turnover marker measurements, may be used to improve medication adherence. In a British study, review of results of serial BMD and/or bone turnover marker measurements between nurse and patient, or doctor and patient, resulted in improved adherence to, and persistence with, medication.[20] However, there is no current consensus on the use of surrogate parameters to increase patient treatment adherence. Three major international guidelines recommend follow-up to ensure that treatment is effective. Regular monitoring is an important component of any osteoporosis treatment plan.[21–23] This applies to at-risk patients whether or not they are on bone-protective drug treatment. Follow-up BMD testing and physician check-ups are also recommended.[21–23]

Patients with an increased risk of fracture at initial examination should be re-evaluated at regular intervals for implementation of non-pharmacological measures, risk factors, and fracture risk. Because a decrease in BMD below measurement error before two years is unlikely, follow-up BMD examinations are usually not recommended at intervals of less than two years.[24] Repeat DXA scans at intervals of two years or longer are appropriate when the efficacy of treatment, risk assessment, or decision to change or interrupt treatment is being considered.[24] Repeat scans may also be useful for addressing patient concerns in relation to treatment adherence. Change in BMD may be difficult to interpret if less than the precision error (2.8×precision measured as the standard deviation or

coefficient of variation of repeat measurements). Pretest probability, as well as concordance of change at different skeletal sites, assists in determining a significant change.

After initiating a specific pharmacological intervention, clinical examinations are recommended after 3–6 months and after 6–12 months. This may include documenting pain, functionality, weight, and height.[22] Ongoing monitoring of patients taking medication, particularly those taking oral bisphosphonates, should be conducted to ensure adherence with administration instructions. Laboratory tests may be used to identify drug-induced side effects or potentially treatable conditions contributing to the patient's bone health (e.g., low vitamin D or thyroid disease).

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Special issues

Management of osteoporosis in frail and older people (over 75 years of age)

Management of osteoporosis in frail and older people (over 75 years of age)

Recommendations

Recommendation 36	Grade
Consider a multifactorial approach (environment, pharmacological treatments, exercise, nutrition) to reduce falls and fracture risk.	C

Introduction

Despite the high absolute fracture risk in the older adult population, there is limited evidence-based literature, RCTs, and studies with fractures as an outcome in frail and older people (defined as aged >75 years for the purpose of this document). This group is at the highest risk of fracture, with hip fracture the most common fracture type.[1,2]

Few studies include patients aged >75 years and, if they do, the numbers are often small and they are infrequently analysed as subgroups. Most of the evidence is based on a systematic review.[3] Reassuringly, a review of the published literature on the clinical efficacy and safety of specific osteoporosis treatments in reducing fracture risk in women aged ≥75 years confirms the benefit of treatment.[4–15] A consensus statement has recommended there is sufficient evidence for pharmacological treatments for the prevention of osteoporotic fracture in residential aged care.[16] (Refer to **Sections 3.1**, **3.2**, **3.3**, and **3.5** for evidence updates on bisphosphonates, denosumab, romosozumab, and teriparatide, respectively).

Denosumab is the only agent for which RCTs have been specifically designed and powered to demonstrate a benefit in the reduction of hip fracture risk in women aged >75 years.[11–13,15] Risedronate has been demonstrated to be beneficial in a mixed cohort of patients aged between 70 and 100 years with osteoporosis, but not in those aged >80 years with risk factors only.[5–7]

For non-vertebral fracture, there is evidence for fracture risk reduction with zoledronic acid in those aged ≥75 years,[10] and with risedronate in those aged 70–79 years.[5] There are inadequate conclusive data for most other agents in terms of non-vertebral fracture risk reduction in older populations because this subgroup is not specifically reported.[14,15]

Antiresorptives and osteoanabolic agents (romosozumab and teriparatide) are considered effective for vertebral fracture risk reduction in older female populations.[3–16]

Studies of the osteoanabolic agent romosozumab (compared with placebo or active comparators) have included a large proportion (30–50%) of patients aged >75 years. Although there is evidence for benefit in the total cohort (age 55–90 years) in improving BMD,[17–20] vertebral fracture risk,[17,18] clinical fracture risk[19,20] and non-vertebral fracture risk,[19] the benefit in those specifically over 75 years was not reported. However, there is no reason to doubt its efficacy in older people.

A Cochrane review of data pooled from 14 studies (11,808 participants) conducted in residential care settings found moderate-quality evidence for a small reduction in hip fracture risk (RR 0.82; 95% CI: 0.67–1.00) for hip protectors.[21] The absolute effect was 11 fewer people (95% CI: from fewer than 20 to 0) per 1000 having a hip fracture when provided with hip protectors. There was moderate-quality evidence when pooling data from five trials in the community (5614 participants) that showed little or no effect on hip fracture risk (RR 1.15; 95% CI: 0.84–1.58) with hip protectors.[21]

Practical tips and precautions

- Frail and older people aged >75 years are at the highest risk of minimal trauma fracture. It is essential to assess bone health and BMD, if indicated. (Note: BMD testing is Medicare subsidised for those with risk factors, those aged >70 years and those with a fragility fracture. See **Appendix C**.)
- Frail and older people have unique needs and differ from younger populations in fragility fracture risk.
- It is important that clinicians apply a multifactorial and multidisciplinary approach for effective fracture reduction in frail and older people, rather than just relying on bone-protective medications.[22]
- It is essential to address the triad of osteoporosis, falls risk and reducing the impact of falls in frail and older people[15] (refer to **Sections 2.2** and **2.3**).
- A safe environment (extrinsic) and minimising intrinsic factors (comorbidity, medications and polypharmacy) are critical to reducing falls risk.
- Encourage safe mobility and exercise under appropriate supervision[15] (refer to **Section 2.3**).
- Optimise nutrition, particularly protein, calcium and vitamin D status, because frail and older people are more likely to be deficient due to poor dietary intake, malabsorption or inadequate sun exposure (vitamin D). Supplementation can be considered. Refer to **Sections 2.1** and **2.2**.
- Choose anti-osteoporosis medications based on patient factors, including medication adherence and persistence factors[15] (refer to **Section 3**).
- FLSs and early, multidisciplinary intervention after fracture are cost-effective strategies to reduce recurrent fracture risk.[22]

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Bone loss associated with aromatase inhibitor therapy for breast cancer and androgen deprivation therapy for prostate cancer

Bone loss associated with aromatase inhibitor therapy for breast cancer and androgen deprivation therapy for prostate cancer

Most patients with a diagnosis of early oestrogen receptor (ER)-positive breast cancer or localised prostate cancer now have a good prognosis, with 10-year survival rates greater than 90% (pbs.gov.au (https://www.pbs.gov.au/pbs/home)). Survivorship issues such as unfavourable cancer treatment effects on bone health are of paramount importance. Endocrine treatments improve cancer-specific outcomes, but lead to severe hypogonadism, and therefore accelerated bone loss.

Recommendation 37	Grade
All women commencing aromatase inhibitor therapy should have baseline assessment of fracture risk prior to commencing therapy, including clinical risk factors, biochemistry and BMD (DXA) measurement, with ongoing monitoring based on risk factors.	A

Baseline assessment includes review of clinical risk factors, blood and urine laboratory testing (electrolytes, calcium, alkaline phosphatase and 25(OH)D) and DXA BMD measurements.[1] If reduced bone mass is present at baseline, individualised assessment is necessary to identify unrelated secondary causes of osteoporosis.

In all postmenopausal women, and in premenopausal women with a Z-score of ≤−1.5, subclinical vertebral fractures should be excluded either by vertebral fracture assessment as part of DXA or by plain radiographs of the thoracolumbar spine. Vertebral fractures are defined by the PBS as a 20% or greater reduction in the height of the anterior or mid-portion of a vertebral body relative to the posterior height of that body. This is important because evidence suggests that spinal fractures are often the first fracture to occur in osteoporosis, increase the risk of future fragility fractures, and are mostly clinically silent.[2]

Although risk calculators such as FRAX® may be useful, they do not consider aromatase inhibitor use and may substantially underestimate fracture risk.

Clinical risk factors for osteoporosis in cancer, including breast cancer

- High prevalence of vitamin D deficiency[3–5]
- Decreased physical activity[6,7]
- Increased risk of falls secondary to treatment-induced neuropathy[8]
- Chemotherapy-induced ovarian failure[9]
- Aromatase inhibitor therapy[10,11]

Recommendation 38	Grade
Women commencing aromatase inhibitor therapy who fall within one of the following two categories should commence antiresorptive therapy unless contraindicated: • age ≥70 years with BMD T-score ≤−2.0 • age >50 years with a minimal trauma fracture (including radiological vertebral fracture) or a high estimated 10-year fracture risk. There is limited evidence specific to women receiving aromatase inhibitors to guide firm recommendations outside these criteria, especially in premenopausal women.	A

Australasian[1,3] and international consensus guidelines[9,12] recommend antiresorptive therapy should be initiated in aromatase inhibitor-treated women not fulfilling the above criteria if the lowest BMD T-score is ≤−2.0 or if more than two fracture risk factors are present, and that it should be considered where

there is a greater than 5–10% decrease in BMD after one year of aromatase inhibitor treatment or if the 10-year absolute risk of a major osteoporotic fracture is ≥20% or that of a hip fracture is ≥3%. However, this is outside current Australian PBS subsidy criteria.

Premenopausal women commonly have normal baseline BMD with low short-term fracture risk, yet lose bone more rapidly than older postmenopausal women. Decisions regarding antiresorptive treatment should be individualised and discussed with the patient. Bisphosphonates can persist in the bone matrix for years after therapy is discontinued, potentially resulting in fetal exposure during pregnancy. Specialist referral may be appropriate.

Recommendation 39	Grade
The duration of antiresorptive treatment in women undergoing or who have completed aromatase inhibitor therapy should be individualised and based on absolute fracture risk.	D

Bone loss in women is most marked in the 12–24 months after initiation of aromatase inhibitor treatment. Limited data suggest partial BMD recovery after cessation of aromatase inhibitor treatment. DXA should be repeated 12 months after commencement of aromatase inhibitor therapy, with subsequent individualised monitoring frequency.

Recommendation 40	Grade
General measures to prevent bone loss should be implemented in all women commencing aromatase inhibitor therapy.	C
Recommendation 41	**Grade**
All men commencing ADT should have a baseline assessment of fracture risk, including BMD assessment by DXA.	A

Key recommendations for the management of bone health in men receiving ADT are adapted from previously published management guidelines of the Endocrine Society of Australia, the Australian and New Zealand Bone and Mineral Society, and the Urological Society of Australia and New Zealand.[13]

Risk factors for osteoporosis should be ascertained, basic laboratory testing should be conducted (electrolytes, calcium, alkaline phosphatase, and vitamin D) and hip and spine BMD measurements should be determined by DXA. Linkage of deidentified Australian MBS and PBS databases recently showed that approximately 80% of Australian men commencing ADT for prostate cancer were not referred for a DXA scan.[13] Absolute baseline fracture risk may be estimated using mathematical tools such as FRAX® or Garvan Fracture Risk Calculator. However, neither of these algorithms is validated in men with prostate cancer receiving ADT, and the tools may underestimate true fracture risk. In men with a T-score ≤−1.0, thoracolumbar spine X-rays should be performed to exclude clinically silent vertebral fractures.[14] DXA should be repeated 12 months after commencement of ADT, with subsequent individualized monitoring frequency.

Recommendation 42	Grade
All men receiving ADT with a history of minimal trauma fracture should be commenced on antiresorptive therapy, unless contraindicated.	A

There is currently insufficient evidence to make evidence-based recommendations regarding if, and when, antiresorptive therapy for primary prevention should be commenced in men with prostate cancer receiving ADT. Consistent with general recommendations in this guide, all men aged ≥70 years with a T-score ≤−2.5 should commence antiresorptive therapy, and therapy should be considered if there is an annual BMD loss of 5–10% or a 10-year absolute risk of major osteoporotic fracture ≥20% or that of hip fracture ≥3%.

Australian guidelines recommend that antiresorptive therapy should be considered for primary prevention if the BMD T-score is ≤−2.0.[15] However, this recommendation is outside current PBS subsidy criteria. Although antiresorptive therapy is recommended (and subsidised by the PBS) for primary fracture prevention in glucocorticoid-induced osteoporosis when the T-score is ≤−1.5, current evidence is insufficient to recommend the same or similar T-score cut-off for men receiving ADT.

Recommendation 43	Grade
Bone health should be reviewed 1–2 yearly in men on continuous ADT.	C

Management should also be re-evaluated after cessation of ADT, because the gonadal axis may recover in some men, with more rapid recovery reported in younger men (<65 years) or in those with a shorter (<24–30 months) duration of ADT.[15]

Recommendation 44	Grade
General measures to prevent bone loss should be implemented in all men commencing ADT.	C

For both women and men commencing and during aromatase inhibitor therapy or ADT, skeletal health should be considered in the decision-making process regarding the choice and duration of endocrine therapy. Skeletal health should be assessed regularly and non-pharmacological intervention optimised.[1]

Evidence statement

Evidence Statement

Aromatase inhibitor therapy

Adjuvant endocrine therapy, either with SERMS, such as tamoxifen or aromatase inhibitors, is generally given for 5–10 years. Tamoxifen has partial ER agonist activity in bone and is protective in postmenopausal women, but leads to accelerated bone loss in premenopausal women. Aromatase inhibitors block oestradiol production, reducing circulating oestradiol by >98%. Aromatase inhibitors inhibit oestradiol-mediated negative feedback on gonadotropin production. They cannot be used in premenopausal women unless ovarian function is suppressed, typically by pharmacological or surgical means.[16–18]

In postmenopausal women, aromatase inhibitors are preferred because of modest improvements in breast cancer outcomes compared with tamoxifen.[19] Although endocrine treatment in premenopausal women is evolving, the use of ovarian suppression plus an aromatase inhibitor is becoming more frequent, especially in younger women (<35–40 years) with high-risk breast cancer.[20]

In postmenopausal women, aromatase inhibitors are associated with a two- to threefold accelerated decline in BMD and bone loss is greatest within the first two years. Approximately 10% of untreated postmenopausal women will have a new clinical fracture within three years of aromatase inhibitor treatment.[21] In premenopausal women, bone loss is even higher, with rates of 7–9% in the first 12 months; after five years of treatment, 13% of women have osteoporosis by DXA criteria.[20] In RCTs, bisphosphonates prevented aromatase inhibitor-induced bone loss, but the studies were not powered for fracture end points.[22–25] In contrast, a large trial reported a 50% reduction in clinical fracture rates with denosumab (60 mg given six-monthly for three years) compared with placebo in postmenopausal women.[21]

Of note, given the rapid offset of denosumab action and risk of rebound vertebral fractures, delays in the six-monthly administration should be avoided and, according to current evidence, a course of denosumab treatment needs to be followed by a bisphosphonate (refer to **Section 3.2**). Women should be informed about this prior to starting treatment.

Androgen deprivation therapy

Although testosterone is important for bone health due to direct effects on the male skeleton, a large proportion of its bone-protective actions are indirect, via aromatisation to oestradiol. In addition, testosterone improves bone strength through anabolic effects on muscle mass. Loss of muscle increases fracture risk due to a higher propensity for falls.[7] ADT usually involves depot preparations of gonadotropin-releasing hormone (GnRH)

analogues and reduces sex steroids to castrate levels. Newer treatment modalities, such as abiraterone, also inhibit extratesticular sex steroid synthesis and lead to even more profound sex steroid deprivation.[26,27]

Low BMD is highly prevalent among men even prior to commencement of ADT, and under-recognised. A study among 236 Australian men (mean age 70 years) with prostate cancer newly commencing ADT showed that, at baseline, 11% had osteoporosis and 40% had osteopenia.[28] Sixty-one percent of the men with osteoporosis were unaware of the diagnosis. Even in the absence of ADT, bone health is a concern in older men with prostate cancer.

During the first year of ADT, BMD loss is accelerated by two- to sevenfold relative to the 0.5–1% bone loss occurring in ageing men.[12] DXA may underestimate ADT-associated bone loss, especially the loss of cortical bone, which can exceed 10%.[29] BMD continues to decline with long-term ADT, albeit at a lower rate. Large registry studies have shown that ADT increases relative fracture risk by 30–60%.[15] In a cohort study of more than 50,000 men who survived for at least five years after prostate cancer diagnosis, fracture incidence approached 20%, and the number needed to harm for the occurrence of any fracture was 28 for GnRH agonist use and 16 for orchidectomy.[30]

Multiple RCTs have shown bisphosphonate therapy prevents ADT-associated BMD loss, but they were too small to provide fracture outcomes.[15] In contrast, a large RCT in men receiving ADT showed that denosumab reduced the incidence of vertebral fractures (RR at three years 0.38 versus placebo; *P*=0.006) in men receiving ADT with a median T-score of −1.5 at randomisation, with a number needed to treat to prevent one incident vertebral fracture of 42.[31]

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Medication-related osteonecrosis of the jaw

Medication-related osteonecrosis of the jaw

Recommendations

Recommendation 45	Grade
MRONJ is a rare complication of osteoporosis therapy and most patients will not be at increased risk of MRONJ. Consider a patient's risk of MRONJ prior to starting osteoporosis therapy and ensure high-risk patients receive dental review prior to therapy initiation. Given the long *in vivo* half-life of bisphosphonates, there is little benefit to their cessation prior to dental extraction. Invasive dental procedures in patients on denosumab should be performed just prior to the next six-monthly injection because the *in vivo* effect on bone suppression will be waning.	C

MRONJ is defined as an area of exposed bone in the maxillofacial region that has persisted for more than eight weeks in a patient receiving bisphosphonates, denosumab, or anti-angiogenic therapy for cancer, with no history of radiation therapy to the jaws or obvious metastatic disease.[1]

MRONJ occurs at a substantially lower incidence in patients undergoing osteoporosis therapy than in those with cancer being treated with antiresorptives to prevent malignancy-related skeletal adverse events. The reported prevalence is between 1 and 100 per 100,000 patient-years (with a 'ceiling' of 150 per 100,000 patient-years) in patients receiving oral bisphosphonate therapy for osteoporosis, marginally higher than the incidence in the general population.[2–4]

The duration of oral bisphosphonate therapy for osteoporosis is a risk factor for MRONJ, with a mean duration of greater than four years.[5] This may be shortened if the patient is also being treated with long-term glucocorticoids or anti-angiogenic drugs.[1] Compared with patients receiving higher doses of antiresorptives (e.g., zoledronic acid or denosumab) for cancer treatment, the risk of MRONJ for patients with osteoporosis exposed to antiresorptive medications is approximately 100-fold smaller.[1]

The aetiology of MRONJ is uncertain, but appears multifactorial and related to dose and duration of antiresorptive exposure, pre-existing oral disease profile, type of dentoalveolar oral surgery, and genetic polymorphisms.[6]

Because the dose and duration of antiresorptive therapy are of concern in the development of MRONJ, patients who have been on more than four years of antiresorptive therapy are at greater risk of MRONJ. Patients should be educated to inform their dental provider if they are taking antiresorptive agents (bisphosphonates or denosumab).

Invasive dental surgery, including extraction, implant insertion, and limited surgical intervention to treat dental infection/abscess, such as periodontal scaling and endodontic (root canal) therapy, have been associated with osteonecrosis of the jaw.

Consensus recommendations from the American Association of Oral and Maxillofacial Surgeons[1] and the International Task Force on Osteonecrosis of the Jaw[6] state that elective dentoalveolar oral surgery is not contraindicated in patients receiving antiresorptive therapy (bisphosphonate and denosumab) for osteoporosis. However, the identification and treatment of dental disease prior to the initiation of antiresorptive therapy, if possible, is recommended.[6] Patients should be adequately informed of the very low risk of MRONJ.

The American Association of Oral and Maxillofacial Surgeons recommends that if systemic conditions permit, discontinuation of oral bisphosphonates for two months before and three months after elective invasive dental surgery may be considered to lower the risk of MRONJ.[1] This guidance contrasts with that of the American Dental Association and the International Task Force on Osteonecrosis of the Jaw, both of which state there is insufficient evidence to recommend a break from antiresorptive drug therapy, or a waiting period before performing minor oral surgical treatment.[6–8] However, the International Task Force on Osteonecrosis of the Jaw recommends that in those at high risk of MRONJ, pausing antiresorptive therapy following extensive oral surgery should be considered until the surgical site heals with mature mucosal coverage.

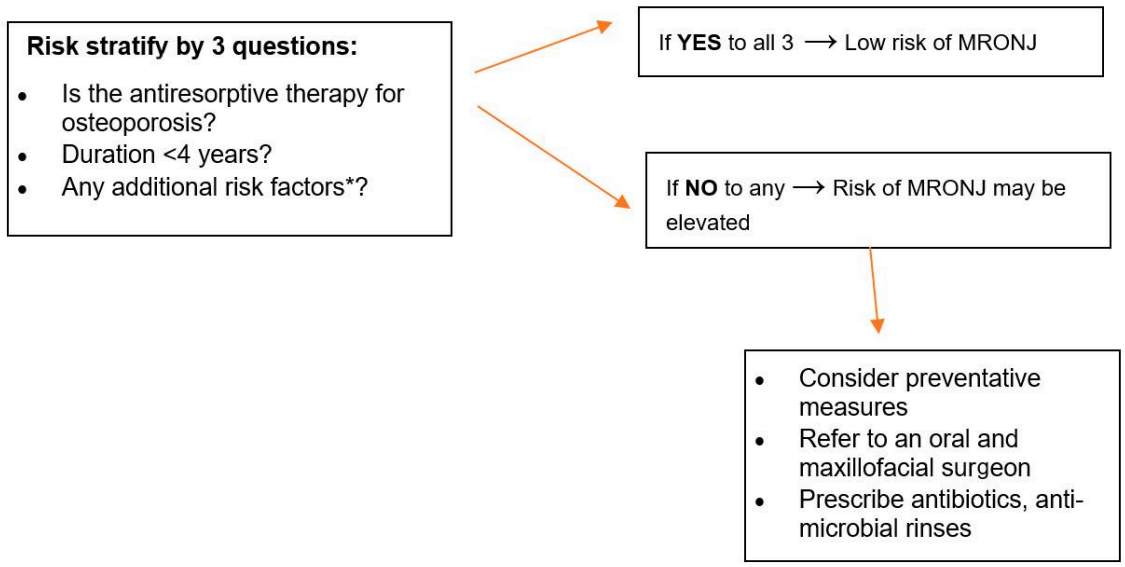
The decision to initiate a treatment pause should be made in consultation with the prescribing clinician and incorporate consideration of the individual patient's fracture risk (refer to **Section 3.2** regarding the risk of rebound vertebral fracture following denosumab cessation). Patients at lower risk of fracture may safely undertake a brief treatment pause if undergoing an invasive dental procedure. There is no evidence to support the use of serum C-telopeptide (a bone turnover marker) to guide the timing of dental procedures in patients receiving antiresorptive therapy.[1,3]

Optimising oral hygiene and addressing active dental disease prior to initiating antiresorptive therapy may reduce the incidence of MRONJ.[6] Good dental hygiene and care are recommended for all patients undergoing antiresorptive therapy for osteoporosis, particularly in those on long-term bisphosphonates. There is a strong association between periodontitis and MRONJ due to the increased likelihood of extractions, the direct effects of bacterial infection, and delayed healing due to inflammation.[8] Improved dental awareness and prophylactic intervention have significantly reduced the incidence of MRONJ in patients receiving antiresorptive therapy for bone-related cancer complications.[9]

However, the benefits of antiresorptive therapy in preventing fragility fractures in patients with osteoporosis and malignancy-related skeletal events significantly outweigh rare adverse events such as MRONJ. Importantly, patients with established MRONJ can be satisfactorily managed and risk minimised. For such patients, referral to a centre with experience in managing and mitigating MRONJ is indicated.

More research to understand the pathophysiology of MRONJ is required, and future recommendations may change to reflect improved knowledge of this condition. However, it is important to be aware of the proven benefits of antiresorptive therapy in fracture risk reduction compared with the very small risk of serious adverse events, such as MRONJ.

Using current evidence, **Figure 2** illustrates key decision points in determining the risk of MRONJ when undertaking a dental procedure and considerations to mitigate this risk.



*Risk factors include poor oral hygiene, smoking, corticosteroids or angiogenesis inhibitors, as well as comorbid diseases such as diabetes and anaemia.

MRONJ, medication-related osteonecrosis of the jaw.

Figure 2

Figure 2. *Practical considerations for patients on antiresorptive therapy undergoing an invasive dental procedure.*[1,2,9]

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Atypical fracture of the femur

Atypical fracture of the femur

AFFs occur in the subtrochanteric region or femoral shaft. AFFs are associated with no trauma or minimal trauma; high-trauma fractures are specifically excluded from this definition.[1] AFFs exhibit several different radiological and clinical features compared with ordinary osteoporotic femoral fractures, in particular a transverse orientation, lack or minimal comminution and localised cortical thickening at the fracture site, which is characteristic of a stress fracture. Bilateral fractures occur in approximately 30% of cases, and prodromal pain in the groin or thigh is a distinguishing feature, occurring in more than 70% of individuals with an AFF.[1]

AFFs appear more common in patients on long-term bisphosphonate therapy and have also been reported following denosumab therapy.[2] A systematic review of 11 studies found that bisphosphonate exposure was associated with an increased risk of AFF, with an RR of 11.78 (95% CI: 0.39–359.69), although the wide CI indicates data heterogeneity, due in part to lack of agreement on the definition of AFF.[3] Although the RR of AFF with bisphosphonate therapy appears on this evidence to be high, the absolute risk remains very low, ranging from 3.2 to 50 cases per 100,000 person-years.[1] However, long-term (over five years) bisphosphonate use is associated with a higher risk of AFF, rising from 2.5 AFFs per 10,000 person-years at five years or less of bisphosphonate use to 13.1 per 10,000 person-years at eight or more years.[4] The evidence also suggests that the risk of AFF may decline when bisphosphonate therapy is stopped, and hence clinicians may consider a ‘drug holiday’ in those receiving long-term bisphosphonate therapy.[1] It is important to stop antiresorptive therapy if an AFF is identified and specialist referral is warranted, as well as radiographic assessment of the contralateral femur, because a proportion of these are bilateral. Specific risk factors for AFF have been identified and include long-term bisphosphonate use, Asian ethnicity, glucocorticoid use, diabetes and previous AFF.[4]

Although epidemiological data are far from conclusive, AFFs are rare, both in the general population (7% occur in patients who have never received antiresorptive therapy) and in patients undergoing bisphosphonate therapy for osteoporosis.[1] The risk of AFF with bisphosphonate therapy must be considered against the far greater incidence of common osteoporotic fractures at all sites and the proven effectiveness of bisphosphonates in reducing osteoporotic fractures.

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Appendix A. Guideline review process

Appendix A. Guideline review process

This guide is an evidence update of the second edition of the clinical guideline Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 years of age published in 2017 by the RACGP and approved by the NHMRC.

This review and updating sought to follow best practice guideline development, but due to limited resourcing some limitations were imposed. Key phases in this review process included:

- establishment of the National Osteoporosis Guideline Review Committee and ongoing register of conflicts of interest (refer to **Appendix D**)
- allocation of sections to review committee members according to their subspecialist bone expertise
- identification of sections requiring additional subject matter advisers and the identification of these experts (refer to **Appendix D**)
- agreement on the scope of work and approach with the RACGP, including use of the existing NHMRC guideline review process and evidence levels system (refer to **Tables 4–6**)
- identification of priority and new subject areas for focused literature search strategies to be performed by the RACGP
- systematic literature searches of these subject areas to identify the primary evidence and syntheses of primary evidence
- appraisal and selection of this evidence by relevant bone experts
- revision and updating of existing content in the guide, as well as drafting new content, sections and/or evidence statements
- revision and updating of current recommendations, as well as the drafting of new recommendations
- full review of final draft guide and agreement on recommendations by the National Osteoporosis Guideline Review Committee
- endorsement of this guide by the RACGP.

Identification, appraisal and synthesis of new evidence

Most recommendations in the 2017 second edition were based on critical analysis of peer-reviewed evidence published between 2006 and 2016, following a systematic review of available evidence to support these recommendations. Every section in this third edition has been reviewed and updated with relevant new peer-reviewed evidence published from 2017 by a bone expert with subspeciality expertise in that topic.

For subject areas identified as requiring new focused published literature searches, the review committee provided specific key words to the RACGP to conduct the search using the following databases: PubMed/Medline, National Institute for Heath and Care Excellence (NICE), Cochrane

database of systematic reviews and Cochrane Central Register of Controlled Trials (CENTRAL), Scottish Intercollegiate Guidelines Network (SIGN), Trip database and Google. Filters were applied in Ovid Medline to identify RCTs, systematic reviews and meta-analyses.[1,2] Other filters applied included men and women older than 45 years of age and studies reporting outcomes of fracture and/or BMD. As far as possible, evidence used to support recommendations covering pharmacological and other interventions for osteoporosis prevention and treatment was restricted to studies with fracture as a primary outcome. However, for some interventions, evidence meeting this criterion was sparse or of variable quality, and high-quality studies with BMD as a primary outcome have been used if, in the opinion of the review committee, the data could be used to support recommendations.

Evidence to support the recommendations was confined to papers complying with Levels I (systematic reviews of Level II studies) and II (RCT or prospective cohort study) of the NHMRC evidence hierarchy. Evidence from cohort and observational studies was used to support some recommendations concerning diagnostic investigations, monitoring, diet and lifestyle, and to update epidemiological and background information.

Table 4. NHMRC evidence hierarchy[3]

Study type	Description
Level I	A systematic review of Level II studies
Level II	An RCT or prospective cohort study
Level III	A pseudo-RCT, case-control study, retrospective cohort study, comparative study with concurrent controls or comparative study without concurrent controls
Level IV	Case series, study of diagnostic yield, cohort study of persons at different stages of disease or cross-sectional study

Adapted from *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines*.[3]
NHMRC, National Health and Medical Research Council; RCT, randomised controlled trial.

Rating of evidence

The body of evidence supporting each recommendation was rated according to the NHMRC body of evidence matrix (**Table 5**). This method is designed to allow for a mixture of components, taking into account the fact that although the body of evidence in any particular area may be small (therefore attracting a low evidence base component rating), a high clinical impact and applicability to the Australian population will merit a high overall rating.

Table 5. NHMRC body of evidence matrix[3]

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias	One or two Level II studies with a low risk of bias or a systematic review of several Level III studies with a low risk of bias	One or two Level III studies with a low risk of bias, or Level I or II studies with a moderate risk of bias	Level IV studies or Level I–III studies/systematic reviews with a high risk of bias

Table 5. NHMRC body of evidence matrix[3]				
Component	A Excellent	B Good	C Satisfactory	D Poor
Consistency	All studies consistent	Most studies consistent, and inconsistency can be explained	Some inconsistency reflecting genuine uncertainty around the clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Populations studied in body of evidence are the same as the target population for the guideline	Populations studied in the body of evidence are similar to the target population for the guideline	Populations studied in the body of evidence differ from the target population for the guideline, but it is clinically sensible to apply this evidence to the target population	Populations studied in the body of evidence differ from the target population and it is hard to judge whether it is sensible to generalise to the target population
Applicability	Directly applicable to the Australian healthcare context	Applicable to the Australian healthcare context with few caveats	Probably applicable to the Australian healthcare context with some caveats	Not applicable to the Australian healthcare context

Adapted from *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines*.[3]
NHMRC, National Health and Medical Research Council.

Grading of recommendations

Each recommendation was given a final grading according to the NHMRC grades of recommendation (**Table 6**). The grading represents the overall strength of the evidence and reflects the confidence with which clinicians can apply a recommendation in a clinical situation. The final grades are based on a summation of individual components of the body of evidence assessment shown in **Table 5**. A recommendation cannot be graded A or B unless the volume and consistency of evidence components are both graded either A or B.

Table 6. NHMRC grades of recommendations	
Grade	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s), but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution* *The review committee also applied a Grade D to recommendations where there is expert consensus in the absence of a strong body of evidence.

Adapted from *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines*.[3]

Consultation and endorsement by the RACGP

Due to resource and time restrictions, the consultation period was focused on Healthy Bones Australia stakeholders and review by the main users of the guide, namely GPs. The National Osteoporosis Guideline Review Committee was particularly cognisant of the importance of clear and pragmatic advice for busy GPs in everyday clinical practice. This guide was reviewed by GP subject matter experts and the RACGP's Expert Committee for Quality Care, and endorsed by the RACGP Board.

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Appendix B: How to use this Guideline

Appendix B: How to use this guide

Recommendations

Each of the **45 recommendations** has been graded from A to D according to the process described in **Appendix A**. The grade reflects the degree of 'trust' that the clinician can place on the clinical application of the recommendation. The National Osteoporosis Guideline Review Committee supports all recommendations and intends they are used in conjunction with clinical judgement and patient preferences. The recommendations do not cover complex medical conditions and comorbidities, nor are they a substitute for individualised specialist advice and/or consultation. The Review Committee supports and encourages dialogue between GPs and specialists, if required for optimisation of patient care.

Recommendations marked with an asterisk (*) underwent a focused detailed published literature search by RACGP library staff, during which the following databases were interrogated to identify publications subsequent to the previous Edition, ie since 2016:

- PubMed/Medline
- NICE
- United States Preventive Services Task Force
- Cochrane database of systematic reviews
- Canadian Task Force on Preventive Health Care
- SIGN
- Trip database
- Google

These were then reviewed by a bone expert with subspeciality expertise in the topic and the relevant chapter(s) updated. The final draft of the chapter(s) underpinning that relevant recommendation(s) was then reviewed by the National Osteoporosis Guideline Review Committee and discussed at two face-to-face meetings.

All other recommendations have been updated by a bone expert with subspeciality expertise in the area and then reviewed by the National Osteoporosis Guideline Review Committee at two face-to-face meetings.

Practical tips and precautions

The practical tips are pointers to effectively implement recommendations. Unless otherwise referenced, the source of information presented in the practical tips is the National Osteoporosis Guideline Review Committee.

Side effects and potential harms

Side effects and adverse events are summarised for each pharmacological intervention. This guide does not seek to provide full safety and usage information on medications. The review committee also recommends consulting the Therapeutic Guidelines (www.tg.org.au (http://www.tg.org.au/)), NPS MedicineWise (www.nps.org.au (http://www.nps.org.au/)) or the *Australian Medicines Handbook* (https://shop.amh.net.au (https://shop.amh.net.au/)) for detailed prescribing information.

Evidence statement

Each recommendation is supported by an updated critical appraisal of current evidence published since 2016. **Appendix A** describes the processes used to review the evidence.

Online resources

- The Royal Australian College of General Practitioners (RACGP). Guidelines for preventive activities in general practice (https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/guidelines-for-preventive-activities-in-general-pr/preamble/introduction) . 9th edn. RACGP, 2016.
- Fracture Risk Assessment Tool: https://fraxplus.org (https://fraxplus.org)
- Garvan Fracture Risk Calculator: www.garvan.org.au/bone-fracture-risk (http://www.garvan.org.au/bone-fracture-risk)
- Therapeutic guidelines: www.tg.org.au (http://www.tg.org.au/)
- NPS MedicineWise: www.nps.org.au (http://www.nps.org.au/)

General information

- Department of Health and Ageing; National Health and Medical Research Council. Nutrient reference values for Australia and New Zealand: Executive summary. Australian Government, 2006.
- Department of Health and Ageing; National Health and Medical Research Council. Eat for health: Australian dietary guidelines. Summary. Canberra: Australian Government, 2013.
- The Royal Australian College of General Practitioners (RACGP). Smoking, nutrition, alcohol, physical activity (SNAP): A population health guide to behavioural risk factors in general practice. 3rd edn. RACGP, 2015.
- The Royal Australian College of General Practitioners (RACGP). Guidelines for preventive activities in general practice. 9th edn. RACGP, 2016.

Resources for patients

- The Healthy Bones Australia website (www.healthybonesaustralia.org.au (https://healthybonesaustralia.org.au)) provides comprehensive, consumer-friendly information for people who have

been diagnosed with osteoporosis, are at risk of osteoporosis or who wish to know more about bone health generally. A range of printable guides and factsheets translated into five languages is available to download from the website.
- 'Know your bones' (www.knowyourbones.org.au (http://www.knowyourbones.org.au/)) is a consumer-friendly, online bone health assessment tool based on the Garvan Fracture Risk Calculator.
- Healthy Bones Australia provides a toll-free consumer helpline: 1800 242 141.

Useful websites

The review committee takes no responsibility for the information provided on these sites or via any links to which they may connect. URL addresses were accurate at time of publication.

- The Royal Australian College of General Practitioners: www.racgp.org.au (https://www.racgp.org.au/)
- Australian Rheumatology Association: www.rheumatology.org.au (http://www.rheumatology.org.au/)
- Carers Australia: www.carersaustralia.com.au (http://www.carersaustralia.com.au/)
- Australian Medicines Handbook: https://shop.amh.net.au (https://shop.amh.net.au/)
- Bone Health & Osteoporosis Foundation (USA): www.bonehealthandosteoporosis.org (https://www.bonehealthandosteoporosis.org)
- Royal Osteoporosis Society (UK): https://theros.org.uk (https://theros.org.uk)
- International Osteoporosis Foundation: www.osteoporosis.foundation (https://www.osteoporosis.foundation)
- Osteoporosis Canada: www.osteoporosis.ca (http://www.osteoporosis.ca)
- Osteoporosis New Zealand: www.osteoporosis.org.nz (https://osteoporosis.org.nz/)

Appendix C: Bone density testing in General Practice

Current MBS items for bone density testing using DXA

HEALTHY BONES AUSTRALIA

Bone density testing in general practice

A guide to Dual Energy X-ray Absorptiometry (DXA)

Scanning of the axial skeleton by dual energy X-ray absorptiometry (DXA) is the gold standard in Australia for the measurement of bone mineral density (BMD). DXA is a diagnostic tool for osteoporosis or osteopenia, enabling doctors to determine the extent of bone loss for clinical decision making. This guide outlines who to refer for DXA and the basics of how to interpret a bone densitometry report. Note the terminology of osteopenia and osteoporosis based on BMD alone in intended for individuals over 50 years of age and menopausal women.

Poor bone health is common in Australia

An estimated 4.7 million Australians over the age of 50 years have osteoporosis or osteopenia, with over 183,000 associated fractures (2022). Early diagnosis and improved management can reduce the current annual cost of $3.84 billion, with fracture costs accounting for up to 67% of overall costs.

In general practice, early detection can prevent a first fracture. For patients who have already fractured, investigation and initiation of osteoporosis medication is crucial to reduce the very high risk of subsequent fractures.

Who to send for a DXA scan

Patients over 50 with risk factors	MBS item
Family history – parent with hip fracture	No rebate
Early menopause	12312
Hypogonadism	12312
Anticipated glucocorticoids ≥4 months ≥7.5mg/day	12312
Coeliac disease/malabsorption disorders	12315
Rheumatoid arthritis	12315
Primary hyperparathyroidism	12315
Hyperthyroidism	12315
Chronic kidney or liver disease	12315
Androgen deprivation therapy	12312
Recurrent falls	No rebate
Breast cancer on aromatase inhibitors	No rebate
Treatment with antiepileptic medications	No rebate
Low body weight	No rebate
HIV and its treatment	No rebate
Major depression/ SSRI treatment	No rebate
Type 1 and type 2 diabetes mellitus	No rebate
Multiple myeloma/monoclonal gammopathy	No rebate
Organ or bone marrow transplant (item 12312 applies if treated with glucocorticoids or if kidney disease present)	No rebate

Patients with a minimal trauma fracture	MBS item
DXA is recommended to establish a baseline BMD for treatment	12306

Suspected vertebral fracture	MBS item
Refer for spinal X-ray when: – Height loss of 3cm or more – Thoracic kyphosis – New onset back pain suggestive of fracture	
If fracture confirmed, therapy indicated, refer for DXA	12306

Vertebral fracture assessment (VFA), also known as Lateral vertebral assessment (LVA) is offered with some DXA scans. VFA may be a useful screen for fractures in people with height loss. MBS rebate not available for VFA.

Patients with osteoporosis	MBS item
T-score equal to or less than -2.5 eligible for one scan every two years	12306

Patients over 70 years of age	MBS item
For men and women over 70 years, MBS rebate applies (regardless of other risk factors)	12320
Patients with a normal result or mild osteopenia (measured by a T-score down to -1.5) eligible for one scan every 5 years	12320
Patients with moderate to marked osteopenia (as measured by a T-score less than -1.5 and above -2.5) will be eligible for one scan every two years	12322

Current MBS items for bone density testing using DXA

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The DXA report

The level of detail provided in a DXA report varies. To comply with guidelines, all reports should state the make and model of the DXA machine used, BMD (measured in g/cm^2), T-score and Z-score. Many DXA reports also provide an Absolute Fracture Risk result.

Medical Imaging Centre – Bone Densitometry Report

Dear Doctor

Re: [Patient] **DOB: .....**

This patient attended on ..... for bone densitometry of AP spine and left hip.

Bone mineral density was measured by [DXA machine make and model]. The results are summarised below:

Scan date: ..... **Sex: Female**

Age at scan: ..... years **Ethnicity: .....**

Scan site	Region	BMD	T-score	Z-score	Change vs Baseline (%)	Change vs last (%)
AP spine	L2-L4	0.890	-2.6	-1.1	##%	##%
Left femur	Total	0.822	-1.5	-0.4	##%	##%
	Neck	0.831	-1.5	-0.0	##%	##%

Absolute Fracture Risk (AFR):

Major Osteoporotic Fracture: 20% | **Hip Fracture:** 3.5%

Risk Factors: None

Trabecular Bone Score (TBS): L1-L4 is #.##

Vertebral fracture assessment: VFA demonstrates a deformity of L3, indicating a probable vertebral fracture. Confirmation with X-ray is recommended.

T-score results
- **-2.5 or lower** is osteoporosis

and
- T-score **between -1 and -2.5** is osteopenia

in over 50s and menopausal women.

Refer to RACGP Guidelines recommendation when individual has minimal trauma fracture*

Z-score
- Useful indicator of increased bone loss
- Particular importance in under 50s
- At any age Z-score **-2.0 or lower** is 'below expected range for age' and should trigger investigation to exclude underlying disease cause bone loss

L1–L4 or L2-L4 usually measured.

Total proximal femur and femoral neck reported. Bilateral hip scans preferable.

This percentage indicates the change in BMD compared to the first scan performed.

FRAX – Absolute fracture risk assessment tool. Most DXA centres can provide this as part of DXA report.

RACGP guidelines recommend treating patients over 50 years with a 10-year result of
- 20% or greater risk of major osteoporotic fracture (MOF)

or,
- 3% or greater risk of hip fracture

TBS – Trabecular Bone Score. Offered by some centers, to assess bone micro-architecture. TBS result can be used to adjust FRAX result. TBS does not attract an MBS rebate.

VFA (vertebral fracture assessment – also known as Lateral vertebral assessment LVA) is offered by some imaging centres. It is a useful screening tool for asymptomatic vertebral fracture. Fractures detected by VFA should be confirmed by plain x-ray. VFA does not attract an MBS rebate.

T-score

Osteopenia	**T-score between -1.0 and -2.5**	BMD between 1.0 and 2.5 SDs below young adult mean
Osteoporosis	**T-score -2.5 or below**	BMD 2.5 or more SDs below young adult mean

The T-score compares the patient's bone density to the peak bone density of young adults. It is the number of standard deviations (SDs) of the BMD measurement above or below the mean BMD of young healthy adults of the same sex. According to the World Health Organisation, osteopenia and osteoporosis can be diagnosed in individuals over 50, and in menopausal women, based on the T-scores.

***NOTE: As outlined in RACGP Guidelines**

Individuals over 50 years with a **low trauma hip or vertebral fracture** are considered to have clinical osteoporosis.

Individuals over 50 years with **other low trauma fractures, and a T-score below –1.5**, (BMD in the lower osteopenic or osteoporotic range), are also considered to have clinical osteoporosis.

Z-score

The Z-score is the number of SDs of the BMD above or below the mean BMD of adults of the same age and sex.

Z-score is a useful indicator of increased bone loss and is of particular importance below 50 years. At any age, a **Z-score -2.0 or lower** is 'below the expected range for age' and should trigger investigation to exclude underlying disease causing bone loss. A **Z-score above -2.0** is 'within the expected range for age'.

www.healthybonesaustralia.org.au

National toll-free number for patients **1800 242 141**

HEALTHY BONES AUSTRALIA Protect Build Support

Current MBS items for bone density testing using DXA

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Appendix D: National Osteoporosis Guideline Review Committee

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Disclaimer

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