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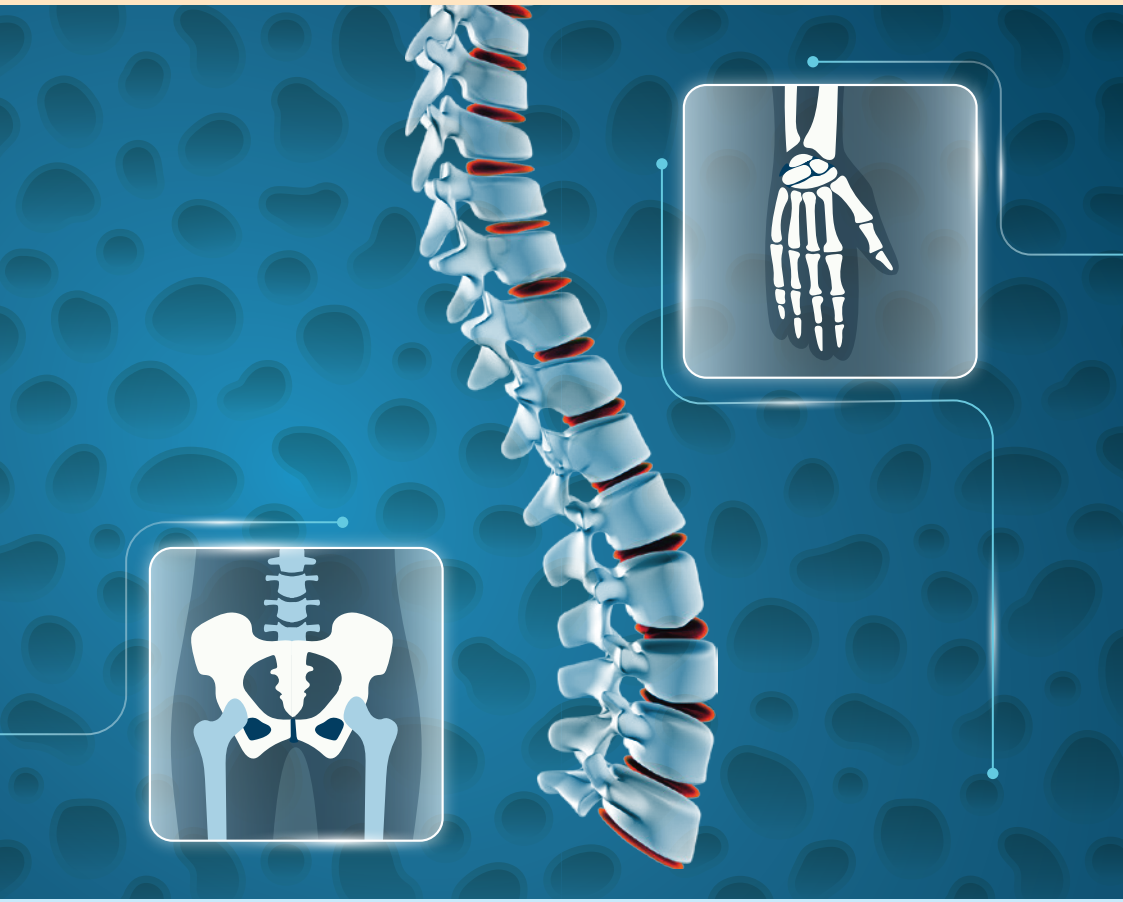
CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF OSTEOPOROSIS

2022 (3RD EDITION)



Academy of Medicine Malaysia

Malaysian Osteoporosis Society

Ministry of Health Malaysia

This revision of the Clinical Guidance on Management of Osteoporosis is now titled as the Clinical Practice Guidelines (CPG) on Management of Osteoporosis. The recommendation in this 3rd edition CPG supersedes the previous Clinical Guidance on Management of Osteoporosis 2015.

STATEMENT OF INTENT

These guidelines are meant for the clinical management of osteoporosis, based on the best available evidence at the time of development. Adherence to the guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the individualised management of his/her patient based on the patient's presentation and management options available locally.

REVIEW OF THE GUIDELINES

These guidelines issued in June 2022 will be reviewed in 5 years (2027) or sooner, if new evidence become available.

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The electronic version is available on the following websites:

http://www.acadmed.org.my

http://www.osteoporosis.my/

https://www.moh.gov.my/index.php/pages/view/3962?mid=1570

FOREWORD

DIRECTOR GENERAL OF HEALTH, MALAYSIA
Tan Sri Dato' Seri Dr Noor Hisham Abdullah

Osteoporotic hip fractures, the worst fragility fracture, are associated with significant disability, morbidity and mortality. Around one-quarter of those who have sustained a hip fracture will not survive beyond 12 months. The International Osteoporosis Foundation has projected that more than half of all osteoporotic hip fractures will occur in Asia by the year 2050. Among the country states of the Asian Federation of Osteoporosis Societies, Malaysia is predicted to have the fastest increase of hip fractures over the coming three decades as we approach the status of an aged nation earlier than projected.

Osteoporosis is a chronic disease closely linked with age. Despite its wide prevalence, osteoporosis remains underdiagnosed and undertreated. Its complication, fragility fractures, is a significant disease burden to the healthcare system and its resources. Hence, those at risk for osteoporosis should be screened to prevent the onset of a first osteoporotic fracture. In addition, those who have already sustained an osteoporotic fracture should receive the necessary treatment to prevent a recurrence, either with effective pharmacological or non-pharmacological therapies.

The 3rd Edition of the Clinical Practice Guidelines (CPG) for managing osteoporosis will reflect best practices and the latest evidence on the management of osteoporosis. It is a condition that crosses traditional speciality boundaries such as endocrinology, rheumatology, orthopaedics, geriatric medicine, family medicine, and rehabilitation. Healthcare professionals such as dietetics and pharmacy are critical in managing osteoporosis. This CPG will be a valuable resource for all healthcare professionals as it covers all aspects of osteoporosis care from identification, diagnosis, risk stratification, treatment, and fracture prevention.

The Ministry of Health congratulates the chairs and the CPG Working Group members for their hard work and believes that this document will further elevate the standard of osteoporosis care and reduce the burden of osteoporotic fractures in our country.

Tan Sri Dato' Seri Dr Noor Hisham Abdullah

PREFACE

CHAIRPERSONS FOR THE CPG WRITING COMMITTEE

With the increasing proportion of older persons in the population, osteoporosis and osteoporotic fractures are growing public health problems worldwide as well as in Malaysia. Thus, to reduce the burden of morbidity and mortality associated with osteoporosis, it is important to treat patients early and effectively. We hope that this practical and evidence-based Clinical Practice Guidelines (CPG) for the Management of Osteoporosis will be useful in that respect.

Since the last CPG revision in 2015, there have been conceptual changes in fracture risk assessment as well as new therapeutic options available. Thus, it is timely that the Malaysian Osteoporosis Society has taken the lead in getting the CPG updated to reflect what should be current best practice. Once again, a multi-speciality panel of experts have come together to form the CPG Working Group, to thoroughly review the literature and produce this latest edition. As with all CPGs, this is not intended to be a fully comprehensive textbook, but a practical guide for clinicians on the latest approach to the assessment, investigation, diagnosis and treatment of patients with osteoporosis, taking into account the availability and accessibility of health care resources.

We would like to thank all the members of the CPG Working Group for their valuable contribution and the external reviewers for their helpful feedback. We hope that the CPG will be useful to all medical practitioners involved in the care of patients with osteoporosis.

Yeap Swan Sim
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CPG Working Group

Terence Ong Ing Wei
Co-Chairperson
CPG Working Group

Lim Lee Ling
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TERMS OF REFERENCE

Guidelines' development

The guidelines development writing committee consisted of rheumatologists, endocrinologists, orthopaedic surgeons, geriatricians, a dietitian, an obstetrician & gynaecologist, and a family medicine specialist.

The previous edition of these guidelines was referred to as "Clinical Guidance". Though it was used as the basis for the development of this document, the writing committee decided to designate these updated recommendations as "Clinical Practice Guidelines".

Literature search was carried out at the following electronic databases: PUBMED, Medline, Cochrane Databases of Systematic Reviews (CDSR), and OVID. In addition, the reference lists of relevant articles were searched to identify further studies. Reference was also made to the latest edition of other guidelines on the management of osteoporosis including the guidelines developed by the International Osteoporosis Foundation (IOF), European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), International Society for Clinical Densitometry (ISCD), World Health Organization (WHO), and National Osteoporosis Foundation (NOF).

Clinical questions were assigned to individual authors. All retrieved literature were critically appraised, presented and discussed. The writing committee agreed with all statements and recommendations. Where the evidence was insufficient, the recommendations were derived by consensus of the committee.

The articles were graded using the SIGN50 format that includes criteria for the levels of evidence and grades of recommendations.

The draft guidelines as a whole were submitted for external review to experts in endocrinology, rheumatology, geriatrics, family medicine, general practice and a lay-person. These guidelines were then presented to the Technical Advisory Committee for Clinical Practice Guidelines and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health, Malaysia for review and approval.

Objectives

The aim of these guidelines is to provide evidence-based recommendations to assist healthcare providers in the identification, diagnosis and management of patients with osteoporosis.

The overarching principle in the treatment of patients with osteoporosis should be to aim at the best care and must be based on a shared decision between the patient and the treating doctor.

Clinical questions

1. In adults, what are the predisposing risk factors for osteoporosis or low bone mineral density?
2. In adults, how is osteoporosis diagnosed?
3. In adults with suspected osteoporosis, what specific investigational modalities will diagnose osteoporosis?
4. In adults with osteoporosis, what are the risk assessment tools available to determine their risk of sustaining an osteoporotic fracture?
5. In adults with osteoporosis on treatment, how can adherence to, and efficacy of treatment be monitored?
6. In adults at risk of or with osteoporosis, are calcium and vitamin D effective for prevention and treatment of osteoporosis?
7. In adults at risk of osteoporosis, what are the life-style measures that can effectively prevent progression to osteoporosis?
8. In adults at risk of osteoporosis, does exercise prevent progression to osteoporosis and risk of falls?
9. In adults with osteoporosis, what are the effective methods for falls prevention?
10. In adults with osteoporosis, what is the ideal time for initiating treatment?
11. In adults with osteoporosis, what are the effective treatment modalities for improving bone mineral density and reducing fracture risk?
12. In adults with osteoporosis and on treatment, particularly bisphosphonates, how would their adverse events affect treatment?

13. In adults with osteoporosis and on treatment, how is treatment failure managed?
14. In adults with glucocorticoid-induced osteoporosis, what are the management approaches to increase bone mineral density and reduce fracture risk?
15. In adults with osteoporosis and renal impairment, what are the special precautions required when treating their low bone mineral density?
16. In adult men with risk of osteoporosis or with osteoporosis, what are the diagnostic and treatment pathways available to improve their bone mineral density and reduce their fracture risk?
17. In adults who have had an osteoporotic fracture, how does a Fracture Liaison Service improve care following treatment of the acute fracture?

Target population

These guidelines are applicable to all adults at risk of developing and with osteoporosis.

Target audience

These guidelines are meant for all healthcare professionals involved in managing patients with osteoporosis such as medical officers, family medicine specialists, primary care physicians, general practitioners, public health physicians, general physicians, endocrinologists, rheumatologists, orthopaedic surgeons, gynaecologists and geriatricians, as well as allied health professionals such as nurse specialists, pharmacists, dietitians and physiotherapists.

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The following experts were invited to provide feedback on these guidelines and are listed in alphabetical order

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LEVEL OF EVIDENCE AND GRADES OF RECOMMENDATION

Levels of evidence

1++	High quality meta-analyses, systematic reviews of RCTs, **OR** RCTs with a very low-risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low-risk of bias
1-	Meta-analyses, systematic, or RCTs with a high-risk of bias
2++	High quality systematic reviews of case-control or cohort studies
2+	Well conducted case control or cohort studies with a low-risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high-risk of confounding or bias and a significant risk that the relationship is not casual
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

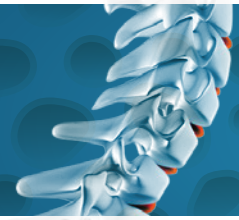
RCT, randomised controlled trial.

Grades of recommendation

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; **OR** A body of evidence consisting principally of studies rates as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results **OR** Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rates as 2+, directly applicable to the target population and demonstrating overall consistency of results **OR** Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 **OR** Extrapolated evidence from studies rated as 2+
☑	Good practice points – Recommended best practice based on the clinical experience of the guidelines development group

RCT, randomised controlled trial.



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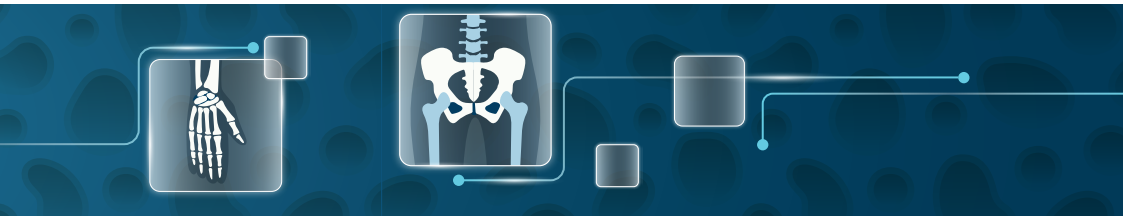


Tables and figures

KEY STATEMENTS AND RECOMMENDATIONS

A clinical diagnosis of osteoporosis can be made after a low-trauma (equivalent to a fall from standing height or less) spine or hip fracture (regardless of bone mineral density).

GRADE C

Osteoporosis is diagnosed based on a T-score of -2.5 or lower on bone mineral density (BMD) measurement by dual-energy X-ray absorptiometry (DXA) at the femoral neck, total hip, or lumbar spine.

GRADE A

Screening for osteoporosis is recommended for individuals with prior low-trauma fractures, those with clinical risk factors, secondary osteoporosis, height loss and falls risk, and for all postmenopausal women ≥50 years old.

GRADE D ☑

Appropriate investigations are recommended to confirm the diagnosis of osteoporosis, determine its severity, exclude secondary causes, and to guide treatment.

GRADE D ☑

BMD measurement with DXA remains the gold standard for the diagnosis of osteoporosis.

GRADE D ☑

The use of quantitative ultrasound (QUS) in the diagnosis and monitoring of treatment in osteoporosis is not recommended.

GRADE D ☑

Bone turnover markers (BTM) are useful for clinical monitoring of treatment response and assessment of adherence to treatment.

GRADE D ☑

All patients commenced on active anti-osteoporosis therapy should be assessed for response to treatment.

GRADE D ☑

Adequate calcium and vitamin D is important for peak bone mass attainment and osteoporosis prevention in adults.

GRADE A

Regular physical activity, in particular weight-bearing exercise is encouraged in all age groups to maximise peak bone mass, decrease age-related bone loss, maintain muscle strength and balance.

GRADE C

Exercise and physical therapy are recommended to prevent falls and injuries from falls.

GRADE A

All older persons ≥65 years old should be screened at least once a year for their risk of falls.

GRADE B

Those at risk of falls should receive a multifactorial falls risk assessment and intervention.

GRADE A

Hip protectors used in care home residents can reduce the risk of hip fractures.

GRADE B

All individuals with osteoporosis should have optimisation of their calcium and vitamin D intake and life-style intervention together with pharmacological therapy.

GRADE A

Very high-risk individuals should be considered for treatment with an anabolic agent if available. Other alternatives (in order of preference) include denosumab or parenteral bisphosphonates.

GRADE B

High-risk individuals should be treated with anti-resorptives (e.g. bisphosphonates or denosumab).

GRADE A

Low-risk individuals should be considered for menopausal hormone replacement or selective estrogen receptor modulators, if clinically indicated.

GRADE B

Table I. The strength of recommendations concerning interventions in the treatment of osteoporosis

Intervention	BMD Improvement	Decrease Vertebral Fracture Rate	Decrease Hip Fracture Rate
Alendronate	A	A	A
Calcitriol / alfacalcidol	A	A	C
Calcium	A	A	-
Calcium + vitamin D	A	-	A
Denosumab	A	A	A
Ibandronate	A	A	-
Menopausal hormone therapy	A	A	A
Raloxifene	A	A	-
Risedronate	A	A	A
Romosozumab	A	A	-
r-PTH/teriparatide	A	A	-
Tibolone	A	*	-
Zoledronic acid	A	A	A

* Effect seen in post-hoc analysis in selected groups of patients; please also see relevant sub-sections in Section 5 for details and references.

Menopausal hormone therapy offered to symptomatic women <60-years-old and within 10 years of menopause helps prevent and treat postmenopausal osteoporosis.

GRADE A

Women who are one year past their last period may be offered tibolone for the relief of menopausal symptoms and prevention of osteoporosis.

GRADE A

Raloxifene may be recommended for postmenopausal osteoporosis as it reduces new vertebral fractures in women with or without prior fractures.

GRADE A

Bisphosphonates are effective treatments for osteoporosis. The overall risk-benefit ratio of treatment with bisphosphonates for osteoporosis is positive.

GRADE A

Oral bisphosphonates are not recommended for patients with an eGFR <30 ml/min (chronic kidney disease stage 4-5).

GRADE D ☑

Zoledronic acid is contraindicated in patients with eGFR <35 ml/min.

GRADE A

It is recommended to review the efficacy of bisphosphonate treatment after 3-5 years. Continuation of treatment would depend on the treatment response, occurrence of side effects, and future fracture risk.

GRADE D ☑

Recombinant parathyroid hormone (r-PTH/teriparatide) is indicated for individuals with very high risk for fractures or osteoporosis not responding to treatment.

GRADE A

Denosumab is an effective anti-resorptive treatment for osteoporosis especially for those at high risk of osteoporotic fractures.

GRADE A

A denosumab 'drug holiday' is not recommended due to an associated rebound increase in bone turnover and increased risk of multiple vertebral fractures (especially in those at high risk of osteoporotic fractures) when the drug is discontinued.

GRADE B

Treatment reassessment may be done after 5-10 years and those who remain at high fracture risk should either continue denosumab or be switched to other osteoporosis therapies.

GRADE D ☑

If denosumab is stopped, subsequent treatment with another treatment option should be initiated to prevent the rebound increase in bone turnover seen with denosumab withdrawal.

GRADE D ☑

Romozusomab is an anabolic agent for the treatment of osteoporosis especially in patients with a very high fracture risk; preferably in those with low cardiovascular (CV) risk.

GRADE A

Romosozumab is currently not recommended in patients with a history of a CV event within the past one year, and should be used cautiously in patients with high CV risk and only when benefits outweigh risks.

GRADE B

Vitamin D supplementation (at least 800 IU/day) in combination with calcium (1200 mg/day elemental calcium) is recommended for fracture and fall prevention in people above 50 years of age who are at risk of fractures, particularly when initiating active osteoporosis therapies.

GRADE A

Treatment failure can be considered when two or more osteoporotic fractures occur and/or <25% change in BTM and/or worsening BMD during treatment.

GRADE C

Before considering treatment changes, patients need to be assessed for treatment adherence, and for the possibility of secondary osteoporosis.

GRADE B

Osteoporotic hip fractures are best treated by early (<48 hours) surgical intervention.

GRADE B

Osteoporotic vertebral fractures can be initially treated conservatively; vertebral augmentation procedures can be considered in specific circumstances if conservative treatment fails.

GRADE A

All patients starting glucocorticoids and in whom it is anticipated that they will be continuing for more than three months should have an initial fracture risk assessment.

GRADE D ☑

The presence of a previous fragility fracture, BMD measurement by DXA and the glucocorticoid-adjusted Fracture Risk Assessment Tool (FRAX®) scores are used to assess fracture risk in patients on glucocorticoids.

GRADE D ☑

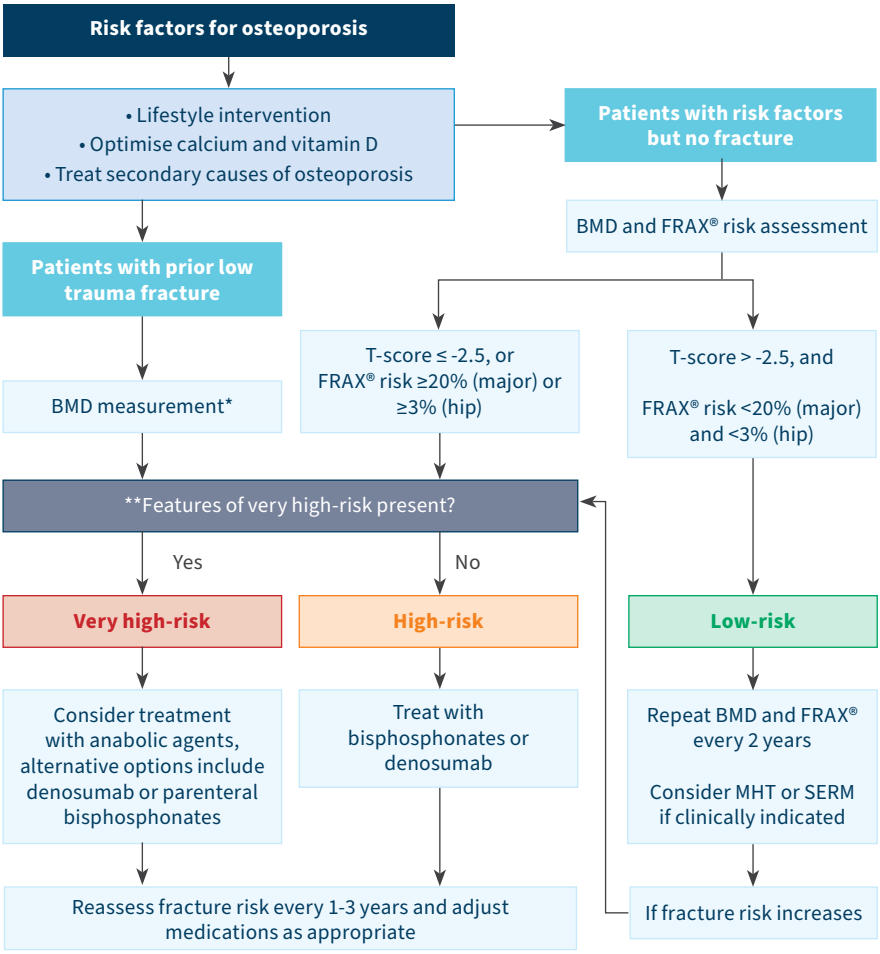
For patients on glucocorticoids with osteoporotic fractures, densitometric osteoporosis and/or very high fracture risk, oral bisphosphonates are the first line treatment.

GRADE A

ALGORITHMS

Algorithm A. Treatment sequence in postmenopausal osteoporosis

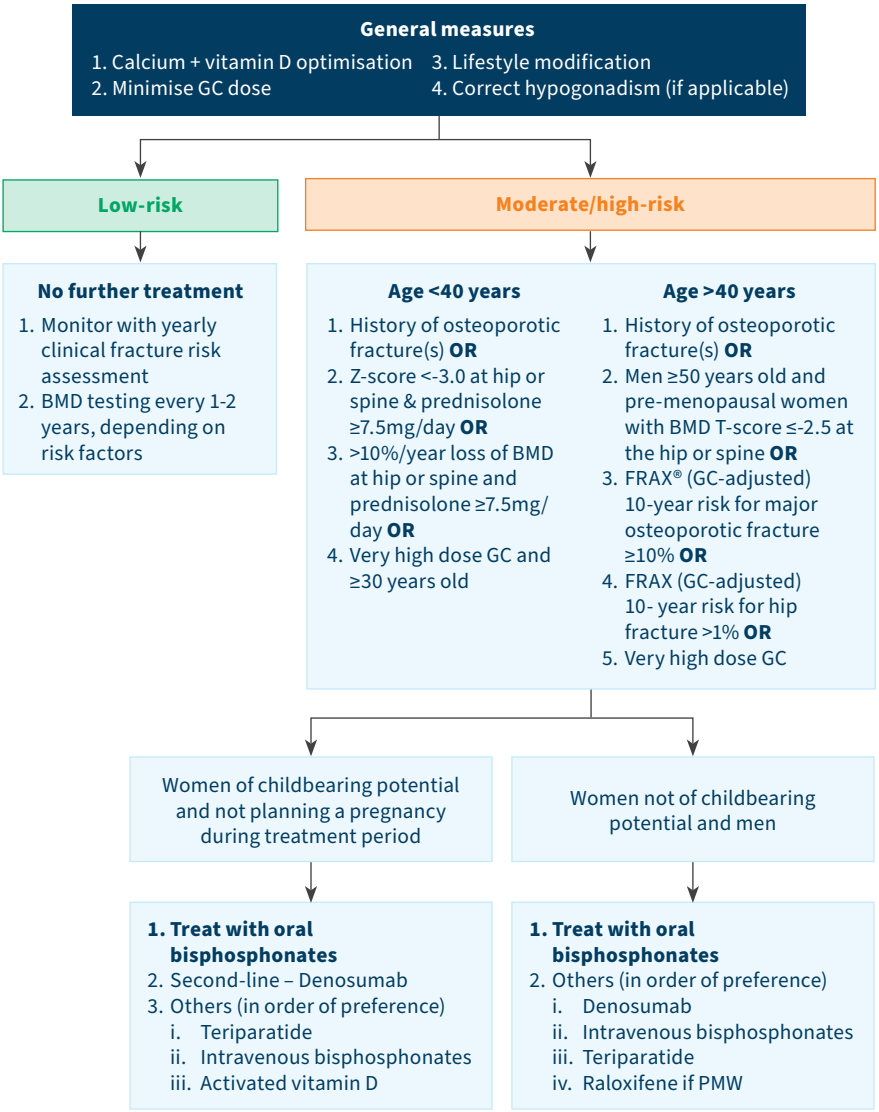
See Section 5



* BMD measurement is not necessary for treatment initiation, but will be useful for monitoring treatment.
** Refer to features of very high-risk in section 5.2.
BMD, bone mineral densitometry; FRAX®, Fracture Risk Assessment Tool; MHT, menopausal hormone therapy; SERMs, selective estrogen receptor modulators.

Algorithm B. Initial pharmacological treatment options in GIOP

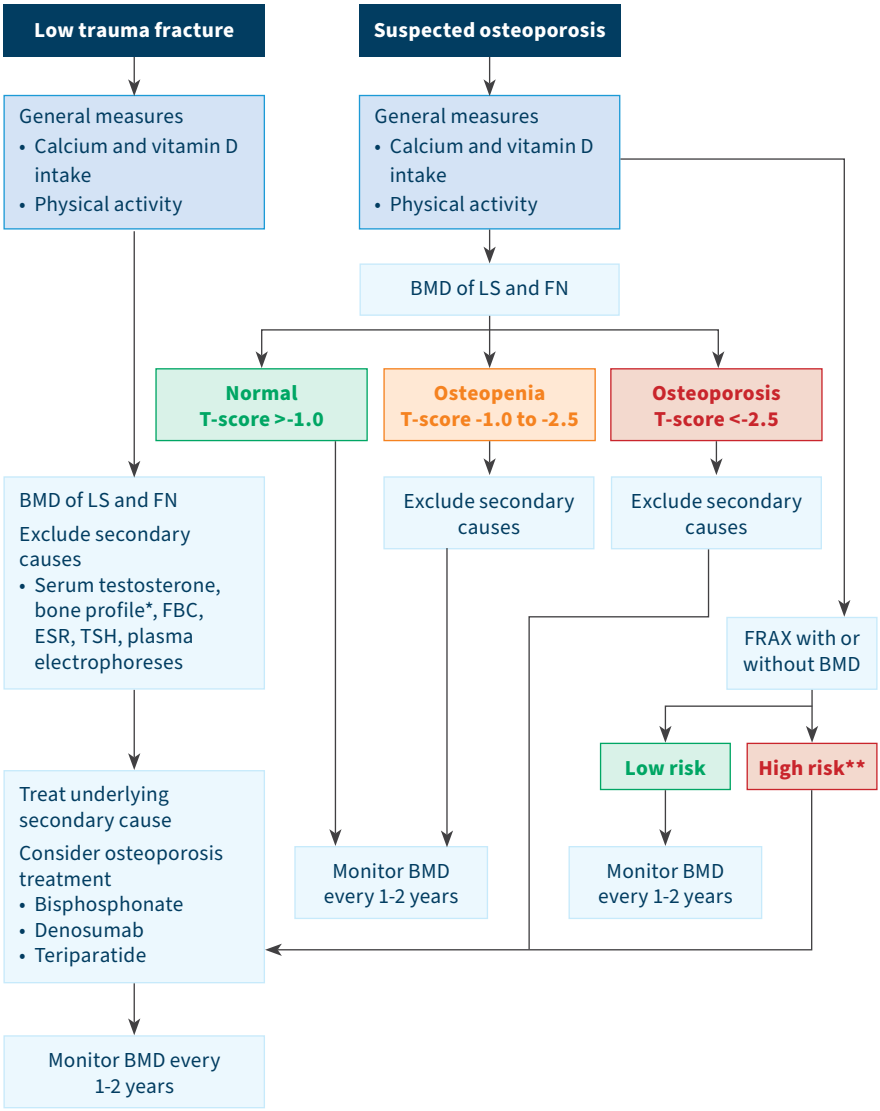
See Section 7



BMD, bone mineral densitometry; FRAX®, Fracture Risk Assessment Tool; GC, glucocorticoid; GIOP, glucocorticoidinduced osteoporosis; PMW, postmenopausal women.
Note: Very high dose GC = treatment with prednisolone (or its equivalent) ≥30 mg/day and a cumulative dose of >5 g in the past year.

Algorithm C. Treatment of osteoporosis in men

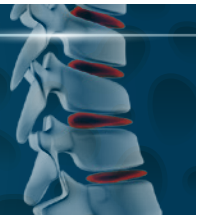
See Section 8



*Bone profile = Calcium, phosphate, alkaline phosphatase, albumin and creatinine; **FRAX® score >20%.
BMD, bone mineral density; ESR, erythrocyte sedimentation rate; FBC, full blood count; FRAX®, Fracture Risk Assessment tool; LS, lumbar spine; FN, femoral neck; TSH, thyroid stimulating hormone.

SECTION 1:

INTRODUCTION



Osteoporosis is defined as a skeletal disorder characterised by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the integration of bone density and bone quality. Bone density (g/cm^2 or g/cm^3) is determined by peak bone mass and amount of bone loss. Bone quality refers to the architecture, turnover, damage accumulation, and mineralisation of the bone.[1]

Osteoporosis-related fractures have been recognised as a major health problem in the elderly. Similar to trends in many countries with increasing life expectancy, Malaysia is expected to have a growing number of elderly individuals. The common sites of fracture are the spine, wrist and hip. Hip fractures are associated with high morbidity and a mortality rate of up to 20% in the first year. Majority of those who survive are disabled and only 25% will resume normal activities.[2,3]

In 1997, the incidence of hip fracture in Malaysia among individuals above 50 years of age was 90 per 100,000. There was a marked increase in the incidence among the older age group. The incidence of hip fracture is consistently higher in women (Table 1-1).[4,5]

Table 1-1. Incidence of hip fracture in Malaysia by age group per 100,000 (1997)

	Incidence by age group (per 100,000)		
Age group	**Male**	**Female**	**Overall**
50-54	10	10	10
55-59	20	30	20
60-64	40	50	40
65-69	60	100	80
70-74	100	230	170
75	320	640	510

Adapted from Lee JK, et al. 2010 APLAR J Rheum.[4]

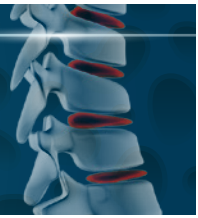
In our community, the Chinese had the highest incidence of hip fractures compared to the Malays and Indians. Chinese women accounted for 44.8% of hip fractures.[4]

The direct hospitalisation cost for hip fractures in 1997 is estimated at RM 22 million and it has been projected to increase to USD 125.4 million by 2050.[6] This is a gross underestimation of the total economic burden, as it does not take into account the costs incurred for rehabilitation and long-term nursing care. Therefore, in an ageing population, the cost of treating hip fractures will escalate without appropriate intervention.[4]

It has been proven that an osteoporotic fracture begets another fracture.[7] This simply means that if a patient has a fracture, the risk of getting a second osteoporotic fracture in the following year is more than double the general population.[8] Hence, appropriate assessment and treatment after the first osteoporotic fracture is vital to prevent the second and subsequent fractures. To improve osteoporosis treatment and fracture prevention, the Fracture Liaison Service (FLS) has been started in hospitals in various countries. FLS encompasses a multidisciplinary team approach to manage patients with osteoporosis and also encourage the patients' siblings and the next generation to start on individual osteoporotic prevention strategies to reduce their risk of fracture (see more in Section 9).

SECTION 2:

CLASSIFICATION AND RISK FACTORS



2.1 Primary osteoporosis

Causes of primary osteoporosis include:

- Postmenopausal osteoporosis – due to accelerated bone loss related to estrogen deficiency
- Age-related osteoporosis – occurs in men and women
- Idiopathic osteoporosis – rarely occurs

2.2 Secondary osteoporosis

Table 2-1 lists some of the causes of secondary osteoporosis.

Table 2-1. Causes of secondary osteoporosis

Endocrine	• Cushing's syndrome • Hypogonadism • Thyrotoxicosis • Primary hyperparathyroidism • Type 2 diabetes mellitus
Drugs	• Glucocorticoids • Heparin • Anticonvulsants (e.g. phenytoin) • Immunosuppressants • Thiazolidinediones • Treatment in oncology (e.g. aromatase inhibitors, androgen deprivation therapy)
Chronic diseases	• Chronic kidney disease • Chronic liver disease • Chronic inflammatory polyarthropathies (e.g. rheumatoid arthritis, systemic lupus erythematosus) • Neurological diseases (e.g. stroke, Parkinson's disease)

Nutrition	• Nutritional deficiency (e.g. anorexia nervosa) • Malabsorption syndrome • Inflammatory bowel disease • Post-gastrectomy/gastric bypass surgical procedures
Others	• Multiple myeloma and malignancy • Osteogenesis imperfecta

2.3 Risk factors for osteoporosis

Osteoporosis is a silent disease without any symptoms in most patients until fractures have occurred. Identification of risk factors will help in case finding.[9] **[Grade D, Level 4]**

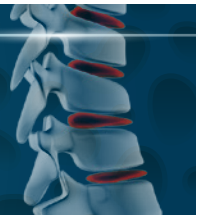
The major risk factors associated with an increased risk of osteoporotic fracture in postmenopausal women are shown in Table 2-2.

Table 2-2. Examples of non-modifiable and modifiable risk factors of osteoporosis[10]

Non-modifiable	Modifiable
1. Advancing age 2. Ethnic group (Oriental & Caucasian) 3. Female gender 4. Premature menopause (<45 years) including surgical menopause 5. Family history of osteoporotic hip fracture in first degree relatives 6. Personal history of fracture as an adult	1. Low calcium and/or vitamin D intake 2. Sedentary lifestyle 3. Cigarette smoking 4. Excessive alcohol intake (≥3 units/day) 5. Excessive caffeine intake (≥3 drinks/day) 6. Low body weight (body mass index <19 kg/m^2) 7. Estrogen deficiency

SECTION 3:

DIAGNOSIS



3.1 Clinical presentation

Most patients are asymptomatic, and diagnosis is made only after a fracture. Common clinical presentations include:

- Increasing dorsal kyphosis (Dowager's hump)
- A low-trauma fracture, i.e.
  - After a fall from standing height or less[11]
  - Fractures occurring at the site of a typical osteoporotic fracture,[12] i.e. at the hip*, spine*, forearm*, humerus, ribs, tibia (excluding ankle), pelvis and other femoral fractures
- Historical height loss of >4cm (>1.5 inches)[13]
- Acute back pain following seemingly innocuous activities, e.g. bending, lifting objects, coughing or sneezing[14,15]

*Most frequent site(s) of osteoporotic fractures.

3.2 Diagnosis

Recommendations

• A clinical diagnosis of osteoporosis can be made after a low-trauma (equivalent to a fall from standing height or less) spine or hip fracture (regardless of bone mineral density)	***Grade C***
• Osteoporosis is diagnosed based on a T-score of -2.5 or lower on bone mineral density measurement by dual-energy X-ray absorptiometry at the femoral neck, total hip, or lumbar spine	***Grade A***

3.2.1 Clinical diagnosis

Osteoporosis can be diagnosed based on clinical presentation where there is a low-trauma fracture (i.e. fragility fracture) in the absence of other metabolic bone disease and where bone mineral density (BMD) assessment may not be feasible or appropriate. A fragility fracture is one that occurs after a fall from standing height or less. Hence, in this situation, treatment should still be initiated.

3.2.2 Bone mineral density (BMD) measurement

BMD measurement via dual-energy x-ray absorptiometry (DXA) at the femoral neck, total hip or lumbar spine remains the **gold standard** recommendation for the diagnosis of osteoporosis.[13,16-18] All patients should have BMD at the lumbar spine (L1-L4, postero-anterior) and hip (to include the femoral neck or total hip) measured. Forearm BMD (1/3rd radius of the non-dominant forearm) should be measured when the hip and/or spine cannot be measured or interpreted, in patients with hyperparathyroidism, and/or in very obese patients (over the weight limit for the DXA table).[19] BMD measurement is also used for determining fracture risk and treatment decisions (see Section 5.2 Risk stratification).

BMD is reported as a T-score or Z-score, both of which are units of standard deviation (SD).

T-score

The T-score represents the number of SDs by which an individual's BMD diverges from the mean value of young female adults. The recommended reference range* for determining the T-score is the United States of America Centres for Disease Control and Prevention's National Health and Nutrition Examination Survey (US CDC NHANES) III database for femoral neck measurements in women aged 20-29 years.[20]

This classification does not apply to premenopausal women, men <50 years old, and children.

*Recommendations from the International Osteoporosis Foundation (IOF), European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), International Society for Clinical Densitometry (ISCD), World Health Organization (WHO), and National Osteoporosis Foundation (NOF).

Table 3-1. The WHO diagnostic categories for osteoporosis

BMD T-score (SD)	Category
-1 and above	Normal bone density
Between -1 and -2.5	Osteopenia
-2.5 and below	Osteoporosis
-2.5 and below, with a prior fragility fracture	Severe osteoporosis

Z-score

The Z-score describes the number of SDs by which the BMD in an individual differs from the mean value expected for age and sex. The Z-score should be used for premenopausal women, men <50 years old and children.

Table 3-2. Z-score definitions

> -2.0	Within the expected range for age
≤ -2.0*	Below the expected range for age

*Consider screening for secondary causes of osteoporosis in premenopausal women and men <50 years old if Z-score is ≤ -2.0.

3.3 Screening

Recommendation

- Screening for osteoporosis is recommended for individuals with prior low-trauma fractures, those with clinical risk factors, secondary osteoporosis, height loss and falls risk, and for all postmenopausal women ≥50 years old

Grade D ☑

Evaluation for the risk of osteoporosis is recommended for all postmenopausal women ≥50 years old and should include detailed history, physical examination and clinical fracture risk assessment with the Fracture Risk Assessment (FRAX®) or other tools (see Section 5.2 Risk stratification).[13,21]

Medical history and physical examination findings suggestive of an increased risk of osteoporosis include:[13]

- Prior fracture (of the hip, spine, forearm, humerus, ribs, tibia excluding the ankle, pelvis and other femoral fractures) without major trauma (after the age of 50 years)[12]
- Clinical risk factors (see Table 2-2)
- Secondary osteoporosis (see Table 2-1)
- Height loss or kyphosis
- Risk factors for falling

Evidence from the SCOOP (Screening for Prevention of Fractures In Older Women) study,[22] a randomised controlled trial involving a community-based screening programme in the United Kingdom demonstrated that the screening of 1000 female

patients aged 70-85 years old prevented nine hip fractures and 20 non-hip fractures over the remaining lifetime (mean of 14 years) compared to usual management. Overall, costs were saved and there was a gain in quality adjusted life-years (QALYs).

3.3.1 Tools for risk assessment

An effective osteoporosis screening tool will be able to reduce the need for DXA scans by prioritising patients at high risk of osteoporosis. Clinical risk assessment tools have been shown to be moderately accurate in identifying risk of osteoporosis and osteoporotic fractures. These include[23] the Simple Calculated Osteoporosis Risk Estimation (SCORE; Merck), Osteoporosis Risk Assessment Instrument (ORAI), Osteoporosis Index of Risk (OSIRIS), Osteoporosis Self-Assessment Tool (OST), and the Malaysian Osteoporosis Screening Tool (MOST).

If available, the use of country-specific fracture risk assessment should be a standard component of investigation to evaluate bone health and predict future fracture and/or osteoporosis risk.[24] In Malaysia, we can use FRAX® for fracture risk assessment, and/or the Osteoporosis Self-Assessment Tool for Asians (OSTA) and MOST as osteoporosis screening tools.

Most of these tools were designed to be used in postmenopausal women. Osteoporosis screening tools to guide further investigation and management for men have been developed as well. These include the Male Osteoporosis Risk Estimation Score,[336] the Osteoporosis Self-Assessment Tool for Men[337] and the Male Osteoporosis Screening Tool.[338] The Osteoporosis Self-assessment Tool and the Male Osteoporosis Screening Tool have been evaluated in a Chinese cohort[338] demonstrating efficacy in ruling out osteoporosis.

Fracture Risk Assessment Tool *(Available at https://www.sheffield.ac.uk/FRAX/)*

FRAX® estimates the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm), for untreated patients between ages 40 to 90 years using clinical risk factors which include an individual's age, sex, weight, height, prior fracture, parental history of hip fracture, smoking, long-term use of glucocorticoids, rheumatoid arthritis and alcohol consumption.[25,26]

The country-specific FRAX® prediction algorithms are available for some countries but not for Malaysia. For Malaysians, we recommend the use of ethnic specific algorithms (e.g. Singapore Chinese or Hong Kong Chinese, Singapore Malay and Singapore Indian) until local data is available.

BMD is not necessary for calculation of fracture probability. However, it improves the prediction of fracture probability. If a BMD is available, only the femoral neck BMD is to be used. BMD input from non-hip sites has not been validated with FRAX® and is, therefore, not recommended.[26]

The treatment interventions in FRAX® have been partly based on cost-effectiveness, for which there is no Malaysian data. Notwithstanding that, we would propose that in patients with osteopenia, initiation of treatment is recommended with a FRAX® (or if available, trabecular bone score [TBS]-adjusted FRAX®) fracture probability of >3% at 10 years for hip or 20% at 10 years for major osteoporosis-related fracture.[13]

FRAX® scores need to be adjusted for glucocorticoid usage – see Table 7-2. For patients with type 2 diabetes mellitus (T2DM), rheumatoid arthritis may be entered into the FRAX® algorithm as a surrogate for fracture risk associated T2DM. Additionally, adjusting FRAX® scores using TBS could be a useful tool for this population.[13]

Malaysian Osteoporosis Screening Tool

MOST calculates the risk of low BMD among women based on age, years since menopause, body mass index (BMI) and hip circumference.[27] It performed well among women (cut-off value ≥4; sensitivity 80.2% and specificity 55.5%) but cannot be used in men.[27] Therefore, there is a paucity of local screening algorithms suitable for Malaysian men and women.[28]

Osteoporosis Self-Assessment Tool for Asians

OSTA is a simple clinical screening tool that is based on age and weight developed for postmenopausal Asian women. Women in the moderate-to-high-risk categories with additional risk factors (see Table 2-2) for osteoporosis should be recommended for DXA.[29]

A meta-analysis of 3 large randomised studies involving a total of 42,009 individuals demonstrated that screening using fracture risk assessment tools (e.g. FRAX®) in women ≥65 years old is effective in reducing osteoporotic fractures and hip fractures, and should be implemented as a prevention strategy.[30]

Measurement of BMD using central DXA should be considered in those found to be at increased risk of fracture[13] (see Section 3.5.1 Densitometry and Appendix 1 for the OSTA chart[31]).

3.4 Investigations

Recommendation

- Appropriate investigations are recommended to confirm the diagnosis of osteoporosis, determine its severity, exclude secondary causes, and to guide treatment — ***Grade D*** ☑

The main aims of investigations are to:[13,17] **[Grade D, Level 4, ☑]**

- Confirm the diagnosis of osteoporosis
- Exclude conditions that can mimic osteoporosis (e.g. osteomalacia and multiple myeloma)
- Assess fracture risk and severity of osteoporosis
- Exclude secondary causes where appropriate, e.g. hyperthyroidism, hyperparathyroidism, Cushing syndrome and hypogonadism
- Determine the most effective osteoporosis treatment
- Determine the baseline measurements for monitoring of treatment response

Appropriate initial investigations are indicated in all patients with postmenopausal osteoporosis. This is to detect any co-existing medical conditions that may cause bone loss as some of these conditions may be asymptomatic (e.g. primary hyperparathyroidism and subclinical hyperthyroidism).[13] **[Grade D, Level 4, ☑]**

Table 3-3. List of investigations[13,17] [Grade D, Level 4, ☑]

Initial investigations
Full blood count (FBC) and erythrocyte sedimentation rate (ESR)
Bone profile (serum) – Calcium, phosphate, albumin
Renal and liver function tests
25-hydroxy vitamin D [25(OH)D] (preferable)
Plain x-rays of the lateral thoraco-lumbar spine (if indicated – to look for asymptomatic vertebral fractures)

Additional investigations that may be indicated on clinical suspicion of secondary causes (see Table 2-1) including:
Thyroid function test
Intact parathyroid hormone (i-PTH)
Serum protein electrophoresis and free kappa and lambda light chains
Morning serum testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH)
24-hour urine calcium and creatinine

Routine plain x-rays are not recommended as radiological osteopenia is apparent in plain X-rays only after >30% of bone loss has occurred.[32]

3.5 Special investigations

Recommendations

- Bone mineral density measurement with dual-energy x-ray absorptiometry remains the gold standard for diagnosis of osteoporosis — ***Grade D*** ☑
- The use of quantitative ultrasound in the diagnosis and monitoring of treatment in osteoporosis is not recommended — ***Grade D*** ☑
- Bone turnover markers are useful for clinical monitoring of treatment response and assessment of adherence to treatment. — ***Grade D*** ☑

3.5.1 Densitometry

T-score determination via the quantified measurement of BMD using DXA is the accepted method for diagnosing osteoporosis (see Section 3.2.1 BMD measurement).

BMD values are also used to establish fracture risk and, determine and monitor management. BMD is still used to establish fracture risk even though ample data show that many patients experiencing fragility fractures do not have a T-score indicating osteoporotic bone density.[19]

Indications for BMD testing[19]

- All adults (≥18 years old) with a fragility fracture
- All adults (≥18 years old) with a disease, condition or taking medications associated with low bone mass or bone loss
- Anyone being considered for pharmacological therapy for osteoporosis
- Those being treated for osteoporosis and to monitor treatment effect
- Anyone not receiving therapy but with evidence of bone loss that would lead to treatment
- All women who are aged ≥65 years and in men aged ≥70 years
- Postmenopausal women <65 years old, women during the menopausal transition, women discontinuing estrogen, and in men <70 years old with clinical risk factors for fracture

Reference database for T-scores[19]

Both the IOF[17] and the ISCD[19] have recommended the use of a Caucasian female normative database for women and men in the calculation of T-scores. However, studies from Malaysia[33] and other Asian countries[34-36] have consistently shown that using a Caucasian database would lead to a higher incidence, thus, resulting in an overestimation of densitometric osteoporosis. Therefore, the Asian database is the default reference dataset for DXA machines in Malaysia.

Central DXA for diagnosis[19]

The WHO international reference standard for osteoporosis diagnosis is a T-score of ≤-2.5 at the femoral neck. In postmenopausal women and men ≥50 years old, osteoporosis may be diagnosed if the T-score of the lumbar spine, total hip or femoral neck is ≤-2.5. In certain circumstances the 33% radius (1/3rd radius) may be utilised. Other hip regions of interest, including Ward's area and the greater trochanter, should not be used for diagnosis.

(See Appendix 2 for further details of the different skeletal sites to measure).

Reporting BMD scores[19]

For BMD reporting in postmenopausal women and men ≥50 years old, T-scores are preferred and the WHO densitometric classification is applicable (see Table 3-1). In females prior to menopause and in men <50 years old, Z-scores are preferred (see Table 3-2) and is particularly important in children. BMD alone cannot be used to diagnose osteoporosis in men <50 years old whilst the WHO diagnostic criteria may be applied to women in menopausal transition.

Serial BMD measurements[19]

Serial BMD measurements can be utilised to:

- Determine the need of treatment initiation in untreated patients in combination with clinical assessment of fracture risk, bone turnover markers (BTM), height loss and TBS
- To monitor response to therapy by determining an increase or stability of bone density, and in individuals following cessation of osteoporosis pharmacologic therapy
- To detect loss of bone density which indicates need for assessment of treatment adherence, evaluation of secondary cause of osteoporosis and re-evaluation of treatment options

Follow-up BMD testing should be done when the results are likely to influence patient management (see Section 3.6).

3.5.2 Trabecular bone score (TBS)

TBS is an analytical tool that evaluates pixel grey-level variations on a lumbar spine DXA image. It captures information relating to the trabecular microarchitecture.[37]

TBS is associated with vertebral, hip, and major osteoporotic fracture risk in postmenopausal women, hip and major osteoporotic fracture risk in men >50 years old, and major osteoporotic fracture risk in postmenopausal women with T2DM.[19]

It can be used in association with FRAX® and BMD to adjust the FRAX®-probability of fracture in postmenopausal women and older men. TBS should not be used alone to determine treatment recommendations in clinical practice.[19] **[Grade D, Level 4, ☑]**

In patients receiving anti-fracture therapy, the role of TBS in monitoring anti-responsive therapy is unclear but is potentially useful for monitoring anabolic therapy.

3.5.3 Quantitative ultrasound (QUS)

The use of QUS in diagnosing and treatment monitoring of osteoporosis is not recommended. **[Grade D, Level 4, ☑]**

Issues with this assessment modality include the diversity of techniques used, the lack of standardisation and unavailability of comparable local normal ranges. However, QUS appears to be a good predictor of fracture in postmenopausal women (hip, vertebral and global fracture risk) and men ≥65 years old (hip and all non-vertebral fracture risk) independent of central DXA BMD.[19]

The criteria for diagnosis, and recommending and monitoring treatment based on QUS are not well established.[38-40]

Women with low QUS results should be referred for BMD measurement. **[Grade D, Level 4, ☑]**

3.5.4 Bone turnover markers (BTM)

BTM are by-products produced from the bone re-modelling process and are indicative of the rate of bone turnover.[41] They can be measured in the urine and serum, and are classified as markers of bone formation or bone resorption (see Table 3-4).

Table 3-4. Classification and type of BTM[41]

Bone formation	Bone resorption
Total alkaline phosphatase**	Hydroxyproline (HYP)
Bone-specific alkaline phosphatase**	Pyridinoline
Procollagen type 1 N-terminal propeptide (P1NP)**	Tartrate-resistant acid phosphatase 5b (TRAP 5b)
Osteocalcin**	Deoxypyridinoline (DPD)**
Procollagen type 1 C-terminal propeptide (P1CP)	Carboxy-terminal cross-linked telopeptide of type 1 collagen (CTX-1)**
	Amino-terminal cross-linked telopeptide of type 1 collagen (NTX-1)**

**Currently available biomarkers in Malaysia.
DPD and NTX-1 are done via urinary samples.

BTM levels show significant and rapid response to changes in turnover rates in response to treatment, compared to treatment responses in BMD as measured by DXA. Hence, BTM are useful for clinical monitoring of treatment response and adherence from the onset of treatment initiation.[42] BTM have also shown usefulness in identifying patients in accelerated bone turnover states and establishing a prognosis for fragility fracture.[43]

BTM levels can be affected by multiple contributors to pre-analytical variability. Factors that can be adjusted and minimised, termed controllable factors, include circadian rhythm variations, food intake, exercise level, alcohol intake, seasonal variation, and medications such as oral glucocorticoids and aromatase inhibitors. Factors contributing to pre-analytical variability that cannot be controlled, known as uncontrollable factors, include age, degree of mobility/immobility, ethnicity, presence of fracture, and menopausal state.[44,45]

Osteoporotic patients presenting with severely elevated initial BTM values (>3 SDs above the mean) are atypical and should prompt a workup for other causes such as,[46,47] a recent fracture, hyperparathyroidism, Paget disease, chronic kidney disease and cancer. **[Grade D, Level 4, ☑]**

Although all BTM can shift in response to osteoporotic disease processes, the IOF and International Federation of Clinical Chemistry (IFCC) have recommended[48] using serum P1NP and CTX-1 as bone formation and resorption markers, respectively, for fracture risk prediction and monitoring osteoporosis treatment (see Section 3.6). **[Grade D, Level 4, ☑]**

3.6 Monitoring therapy

Recommendation

- All patients commenced on active anti-osteoporosis therapy should be assessed for response to treatment — ***Grade D*** ☑

All patients initiated with active anti-osteoporosis therapy should be reviewed within three months to review tolerability. To assess response to treatment, patients should be reviewed at least annually.

Monitoring should encompass assessment for fracture, BMD and BTM (see Table 3-5). **[Grade D, Level 4, ☑]**

Table 3-5. Approaches for monitoring therapy

Monitoring for fractures[21] [Grade D, Level 4 ☑]	• Monitor for clinical or asymptomatic fractures • Clinically evaluate for back pain, recent falls and loss of height • Vertebral or skeletal radiographs – these radiographs are indicated if there is clinical suspicion of fracture (e.g. back pain, recent falls or loss of height)[13,17] • A vertebral fracture assessment (VFA) done during BMD measurement to look for asymptomatic vertebral fractures can be used as well
Monitoring BMD [Grade D, Level 4 ☑]	• Intervals between BMD testing should be determined according to patient's clinical status, typically 1 year after initiation of therapy or change in therapy, and longer intervals once therapeutic effect is established[19] • In conditions associated with rapid bone loss such as glucocorticoid-induced osteoporosis, more frequent BMD monitoring is appropriate[19] • Consider that there has been an adequate response to treatment if, there is a 1-2% increase in BMD/year for up to 3-5 years or a stable BMD[13,21] • A continued loss of BMD of >5% in at least 2 serial BMD measurements at the lumbar spine or >4% at the proximal femur[49] would suggest treatment failure • Monitoring for treatment response using QUS and peripheral DXA is not recommended[19] • The role of TBS in monitoring the effect of anti-resorptive therapy is unclear whilst there is a potential role for it in monitoring anabolic therapy[19]
Monitoring BTM [Grade C, Level 2+]	• Significant reductions in BTM are seen with anti-resorptive therapy and associated with fracture reduction[13,21,50] • Decreases in BTM on anti-resorptive therapy of less than the least significant change (or reference change value [RCV]) is considered "failure of therapy"[51,52] • Significant increases in BTM indicate good response to anabolic therapy[13,21] • A lack of decrease in BTM with bisphosphonates could indicate a lack of compliance or inadequate drug absorption (i.e. taken with calcium/food)

CTX is commonly recommended for monitoring adherence with bisphosphonates and denosumab whilst P1NP has been recommended for monitoring treatment with anabolic agents in clinical practice (see Table 3-6 and refer to Section 3.5.4).

Table 3.6: CTX and P1NP reference change value (RCV)* or least significant change indicating treatment efficacy[53,54] [Grade C, Level 2+]

	RCV for CTX	RCV for P1NP
Bisphosphonates and denosumab	Decrease ≥30%	Decrease ≥20%
Anabolic treatment	Increase ≥45%	Increase ≥25%

*RCV is defined as the smallest difference between sequential laboratory results which is associated with true change.[54] The values in the table have been adapted from the EuBIVAS study.[53]

Guide for timing of BTM tests **[Grade D, Level 4, ☑]**

- Baseline measurement
- One repeat measurement of the same marker 3-6 months after treatment initiation[54]
- Yearly after that if non-compliance, issues with drug absorption or treatment failure is suspected[44,48,54]
- All measurements should be taken at the same time of the day to minimise the effect of diurnal variation and other contributors to pre-analytical variability

Assessing for treatment compliance is crucial at all times throughout the course of treatment. BTM can be used to assess adherence to oral bisphosphonates.

When there is evidence of a lack of response to treatment (e.g. falling BMD or failure to achieve expected changes in BTM), check for compliance to medications and re-examine need to evaluate for secondary causes before determining treatment failure or justifying a change in treatment (see Section 5.13).[55] **[Grade D, Level 4, ☑]**

SECTION 4:
PREVENTION OF OSTEOPOROSIS AND FALLS

4.1 Nutrition

4.1.1 Calcium and vitamin D

Recommendation

- Adequate calcium and vitamin D is important for peak bone mass attainment and osteoporosis prevention in adults and postmenopausal women — ***Grade A***

Meeting adequate calcium intake has the best evidence for peak bone mass attainment in children and adolescents to prevent osteoporosis in later life.[56] **[Grade A, Level 1++]** Increasing calcium intake either by dietary sources or supplements has small non-progressive effects on bone mineral density (BMD) in adults and postmenopausal women. Calcium supplements increased BMD measurements by 0.7-1.8% in one year.[57] **[Grade A, Level 1++]** However, calcium is considered a threshold nutrient which does not confer additional benefits on BMD when recommended levels are obtained.

Adequate vitamin D intake may also be important for peak bone mass attainment in children and adolescents.[56] **[Grade A, Level 1++]**

The recommended nutrient intake (RNI) for calcium and vitamin D according to age-groups are shown in Table 4-1 (see Appendix 3 for examples of calcium content in certain foods).

Table 4-1. RNI for calcium and vitamin D according to age and sex[58]

	Age	Calcium (mg)	Vitamin D (µg)
Adolescent (boys & girls)	16-18 years	1300	15 (600IU)
Men	19-65 years >65 years	1000 1000	15 (600IU) 20 (800 IU)
Women	19-49 years 50-65 years >65 years	1000 1200 1200	15 (600IU) 15 (600IU) 20 (800 IU)
Pregnancy	1st to 3rd trimester	1000	15 (600IU)
Lactation	1st year	1000	15 (600IU)

Vitamin D supplements are available as ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D2 is derived from plant sources and vitamin D3 from animal sources or exposure to sunlight.[59] With daily dosing, vitamins D2 and D3 appear to be equally potent[60] **[Level 1+]** but with intermittent (weekly or monthly) dosing, vitamin D3 appears to be approximately 3-times more potent than vitamin D2.[61] **[Level 1++]**

Blood levels of 25-hydroxy vitamin D [25(OH)D] provide the best index of vitamin D stores. It has been suggested that levels of >20 ng/ml (50 nmol/L) is the minimum level for skeletal health.[62] However, the International Osteoporosis Foundation (IOF)[63] and Endocrine Society[64] recommend 25(OH)D levels of >30 ng/ml (>75 nmol/l) for optimal bone and musculoskeletal health. **[Level 4, Grade D]**

We suggest that all adults who are vitamin D deficient be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week for eight weeks or its equivalent of 6000 IU of vitamin D2 or vitamin D3 daily to achieve a blood level of 25(OH)D above 30 ng/ml,[64] followed by maintenance therapy of 800–1000 IU/day. **[Grade D, Level 4, ☑]**

4.1.2 Body weight

Although low body mass index (BMI) is a recognised risk factor for fragility fractures,[65] recent evidence has challenged the concept that being overweight or obese might lower fracture risk.[66]

4.1.3 Caffeine intake

Caffeine increases faecal and urinary calcium excretion and may induce a negative calcium balance if dietary calcium intake is insufficient.[67] High caffeine intake (>330 mg caffeine/day) has been associated with increased risk of fragility fracture.[68,69] However, the effect of caffeine appears to be mitigated by increasing calcium intake (40 mg calcium for every 177.5 ml cup of coffee).[70] Patients that regularly consume caffeinated drinks should be advised to increase their calcium intake accordingly.

4.1.4 Smoking

Smoking increases osteoporotic fracture risk. Current smokers have the highest risk (Relative Risk [RR]=1.25; 95% CI 1.15,1.36), followed by ex-smokers (RR=1.19; 95% CI 1.12,1.27) when compared to those who have never smoked.[71] **[Grade B, Level 2++]**

4.1.5 Alcohol intake

Excessive alcohol intake (>2 units daily) should be avoided as it has been associated with increased rates of any fracture and osteoporotic fracture in both men and women.[72] **[Grade C, Level 2+]**

4.2 Exercise

Recommendations

- Regular physical activity, in particular weight-bearing exercise is encouraged in all age groups to maximise peak bone mass, decrease age-related bone loss, maintain muscle strength and balance — ***Grade C***
- Exercise and physical therapy are recommended to prevent falls and injuries from falls — ***Grade A***

4.2.1 Exercise for the prevention of osteoporosis

Regular exercise, in particular weight-bearing exercise (e.g. brisk walking and line dancing) is encouraged in all age groups in order to maximise peak bone mass, decrease age-related bone loss, maintain muscle strength and balance.[73-75] **[Grade D, Level 4]** It is important that an individual's health status should be taken into consideration when recommending an exercise programme.

4.2.2 Exercise for falls prevention

(See also Section 4.3)

Studies have shown the benefits of exercise in the prevention of falls which were significant even in the very old (≥80 years).[76] A systematic review that included 116 studies involving 25,160 participants found that exercise reduces the rate of falls by 23% (pooled rate ratio 0.77, 95% CI 0.71,0.83) compared to controls.[77] Multiple exercise component interventions (i.e. combining ≥2 categories of exercise) have shown to reduce rate of falls beyond 12 months,[77,78] effectively prevented falls and reduced fall-related injuries.[76,79,80]

Sufficient intensity and duration of exercise are required for it to be effective.[81] Interventions with a total weekly dose of >3 hours[77,82] that included balance, functional and resistance exercises were particularly effective in reducing the rate of falls[82,83] while programmes primarily involving resistance training, dance, or walking remain uncertain.[77]

However, there is no difference in the effectiveness of exercise on the rate of falls whether the intervention was delivered in a group setting or to an individual alone.[83]

Exercise has also been shown to reduce the likelihood of sustaining a fracture by 26-46%.[80,83,84] These studies included either elements of resistance or strength training, gait and balance exercise, and weight-bearing component. Additionally, there is also uncertainty if certain individual groups would derive more benefit from exercise than others.

Current evidence is unable to make recommendation of one form of exercise over another to reduce the risk of falls and fractures. However, the evidence does support exercise to be an essential part of an individual's management to reduce their risk of falls and falls-related fractures.

4.3 Prevention of falls

Recommendations

- All older persons ≥65 years old should be screened at least once a year for their risk of falls — ***Grade B***
- Those at risk of falls should receive a multifactorial falls risk assessment and intervention — ***Grade A***

All older persons ≥65 years old should be screened at least once a year for:[85,86]

- Falls
- Frequency of falling
- Difficulties in gait or balance

Older adults who are screened positive should receive a thorough assessment of falls risk factors and given interventions to reduce falls risk.

Table 4-2. The risk factors of falls[86-88]

Physical	Behavioural	Environment
• Muscle weakness • Gait and balance deficit • Visual impairment • ≥2 FRID • Chronic medical illness – diabetes, arthritis, stroke, Parkinson's disease • Incontinence • Foot problems (deformity) • Low BMI/ weight loss • Age >80 years • History of falls	• Cognitive impairment • Depression • Fear of falling • Alcohol misuse • Sedentary behaviour	• Environmental hazards – poor lighting, slippery floors, uneven surface • Inappropriate walking aids/ assistive devices • Poor footwear

* FRID were identified according to EUGMS Task and Finish Group such as cardiovascular agents (α-blockers, β-blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme-inhibitors, angiotensin receptor antagonists and vasodilators), CNS drugs (antipsychotics, sedative hypnotics, benzodiazepines, antidepressants, antiparkinsonians, antiepileptics), analgesics (NSAIDs), thyroid drugs and antidiabetics (biguanides, sulfonylureas, other oral hypoglycaemics and insulin.[89-91]

BMI, body mass index; CNS, central nervous system; EUGMS, European Geriatric Medicine Society; FRID, fall inducing drugs; NSAIDs, non-steroidal anti-inflammatory drugs.

4.3.1 Evaluation of falls

A multifactorial falls risk assessment should be performed for all older adults[85,86] with history of falls, who sought fall-related medical attention in the last 12 months or with abnormalities of gait or balance.

Areas of focus during evaluation of falls should comprise of the following parameters (see Appendix 4 for more details):

- A detailed and focused history of fall incidents. In the event of a history of unexplained falls, further assessment will be required
- Review of medications especially those that could increase falls risk
- Assessment or identification of any acute or chronic medical illness
- Assessment and identification of any visual or hearing impairment and its impact on daily living
- Assessment of the person's ability to ambulate, perform activities of daily living, use of assistive devices and support structures
- Examination of gait and balance, the neurological and cardiovascular system

4.3.2 Interventions for falls prevention

Identification of risk factors through a comprehensive multifactorial falls risk assessment would usually identify a number of contributing factors which would require and individualised intervention plan (Table 4-3).[92]

Table 4-3. Assessment of falls risk factors and intervention to reduce identified risk factors[83,93-95]

Assessment	Interventions
Evaluate lower limb muscle strength, gait, and balance *Timed Up & Go* *(high risk >13.5 sec)*	Poor gait, strength and balance • Refer for physical therapy • Engagement in exercise programmes that involve balance, functional exercise and resistance training
Identify medications that increase fall risk	Medication(s) likely to increase fall risk • Optimise medications by stopping, switching or reducing dosage (especially for psychoactive medications)

Assessment	Interventions
Ask about potential home hazards *(e.g. slippery bathroom floor, loose rugs)*	Home hazards likely to increase fall risk • Refer to occupational therapist to evaluate home safety assessment ± modification
Measure positional blood pressure *(supine and standing blood pressure measurement)*	Orthostatic hypotension observed • Review medications • Encourage adequate hydration • Consider use of compression stockings, abdominal binders or physical manoeuvres
Check visual acuity	Visual impairment observed • Refer ophthalmologist/optometrist • Avoid wearing multifocal glasses when walking, particularly stairs
Assess feet and footwear	Feet or footwear issues identified • Appropriate treatment for foot problem identified • Advise wearing well fitted shoes indoors and outdoors
Assess vitamin D intake	Vitamin D deficiency observed or likely • Recommend daily vitamin D (800-1000 IU) supplement for individuals with proven vitamin D deficiency
Previous history of falls OR fear of falling	Provide falls education and information to all patients • Regular follow up to ensure adherence to interventions

The evidence for single component or multicomponent interventions suggests only a modest effect in reducing the rate of falls and fall-related outcomes.[87,96-99] Factors that may contribute to low levels of effectiveness are poor adherence to intervention plans such as difficulties attending appointments to exercise programmes, lack of interest in mitigating home hazards, and refusal for medication modification.

4.4 Hip protectors

Recommendations

- Hip protectors used in care home residents can reduce the risk of hip fractures — ***Grade B***
- Hip protectors can be considered for non-care home residents provided they have the appropriate supervisions and the right level of training in its use — ***Grade D*** ☑

Over 90% of hip fractures result from a fall.[100] Hip protectors reduce, absorb and/or shunt the impact on the hip during a fall to prevent a fracture occurring. They range from a hard shell (hard protectors) to a dense foam padding (soft protectors) which are worn in an undergarment to cover the trochanteric area of the hip. No one type of hip protector has been shown to be superior.

Hip protectors may reduce the risk of hip fractures among older people living in care homes.[101,102] However, its effectiveness involving community dwelling older people were less certain.[102] With appropriate supervision and the right level of training, it may still be an option for those residing in non-care home setting.

Any effectiveness from this intervention is dependent on the older person wearing the hip protector and adhering to it. Though acceptance with hip protectors has been shown to range from 37-72%, and adherence from 20-92%,[103] compliance decreased the longer it was worn.[100]

Barriers to its use include dislike of its appearance, urinary incontinence, unwanted side effects (e.g. skin irritation, abrasion, swelling, abdominal bloating, too hot and discomfort/pain), loss of independence with toileting, cognitive impairment and the effort required to wear it.[100,104] Hence, prescribing hip protectors needs to be accompanied by strategies to aid compliance.

SECTION 5:
MANAGEMENT OF POSTMENOPAUSAL OSTEOPOROSIS

5.1 Treatment initiation

In Malaysia, postmenopausal women should be considered for treatment based on the National Osteoporosis Foundation's (NOF) recommendation[105] if they fulfil any of following, after exclusion of secondary causes of osteoporosis: **[Grade D, Level 4, ☑]**

- Identification of low trauma hip, vertebral, wrist or any other major fragility fracture (clinical or asymptomatic)
- T-score ≤-2.5 at the femoral neck, total hip or lumbar spine on dual energy x ray absorptiometry (DXA)
- In patients with osteopenia (T-score between -1.0 and -2.5) with Fracture Risk Assessment Tool (FRAX®) calculated 10-year fracture probability of >3% for hip and >20% for major osteoporotic related fracture

5.2 Risk stratification

In recent years, guidelines have recommended the risk stratification of patients with osteoporosis into low-risk, high-risk, and very high-risk for fractures.[13,106] These recommendations were made following clinical trials demonstrating the efficacy of anabolic therapies in reducing the fracture risks in very high-risk individuals.[107-110]

Various definitions have been proposed to stratify fracture risks for people with osteoporosis.[13,106] The American Association of Clinical Endocrinologists (AACE) proposed the following features to identify people with very high risk of fracture:[13]

- Recent fracture (within the past 12 months)
- Fractures while on approved osteoporosis therapy
- Multiple fractures
- Fractures while on drugs causing skeletal harm (e.g. glucocorticoids)
- Previous history of injurious falls or high risk of falls
- Advanced age
- Frailty

- Very low BMD measurement (T-score < -3.0)
- Very high FRAX® risk (>30% for major osteoporotic fracture and >4.5% for hip fracture), or other validated fracture risk algorithms

The committee decided to adopt the AACE recommendations until further evidence, especially with regards to risk stratification in our local population, is available.

5.2.1 Management based on risk stratification

Recommendations

• All individuals with osteoporosis should have optimisation of their calcium and vitamin D intake and life-style intervention together with pharmacological therapy	***Grade A***
• Very high-risk individuals should be considered for treatment with an anabolic agent if available. Other alternatives (in order of preference) include denosumab or parenteral bisphosphonates	***Grade B***
• High-risk individuals should be treated with anti-resorptives (e.g. bisphosphonates or denosumab)	***Grade A***
• Low-risk individuals should be considered for menopausal hormone replacement or selective estrogen receptor modulators, if clinically indicated	***Grade B***

- Very high-risk individuals require calcium and vitamin D optimisation, lifestyle intervention, as well as pharmacological treatment for osteoporosis. Treatment with sequential therapy with an anabolic agent followed by anti-resorptive, or intravenous bisphosphonates or denosumab are recommended for these patients **[Grade B, Level 1++]**
- High-risk individuals require calcium and vitamin D optimisation, lifestyle intervention, and pharmacological treatment for osteoporosis. Oral bisphosphonates or other anti-resorptive are recommended as the first line of treatment for high-risk patients **[Grade A, Level 1++]**
- Low-risk individuals can be managed with calcium and vitamin D optimisation, and lifestyle intervention. **[Grade B, Level 2++]** Menopausal hormone replacement (MHT) or selective estrogen receptor modulators (SERM) may be used when indicated **[Grade B, Level 1++]**

5.3 Treatment sequence

Treatment sequence will depend primarily on (see Algorithm A):

- Risk stratification
- Age
- Site of prior fragility fracture
- Patient preference, adherence and tolerability

In patients with very high risk of fractures, anabolic agents (teriparatide and romosuzomab) are most appropriate to promptly reduce fracture risk.[106,110-114] **[Grade B, Level 1+]** Anabolic agents should be followed by an anti-resorptive agent to maintain anti-fracture efficacy[106,112,113] as their treatment is limited to 12-24 months and the efficacy wanes once treatment is discontinued.

A recent fracture (within the past two years) is a stronger predictor of fracture in the following two years (imminent fracture risk) than is an older fracture (>5 years) history. In these patients, active osteoporosis therapies should be initiated without delay, lifestyle changes implemented and calcium and vitamin D intake optimised. **[Grade B, Level 1+]**

In patients with hip and non-vertebral fractures, bisphosphonates, denosumab and anabolic agents can be used while SERM are not recommended. **[Grade A, Level 1++]**

Patient preference, affordability, degree of adherence and tolerance to the side effect profile of the treatment are also important in dictating sequence of treatment used.

5.4 Menopausal hormone therapy

Recommendation

- Menopausal hormone therapy offered to symptomatic women <60-years-old and within 10 years of menopause helps prevent and treat postmenopausal osteoporosis — ***Grade A***

Postmenopausal hormone replacement therapy (HRT) is now called Menopausal Hormone Therapy (MHT). MHT is available as estrogen therapy (ET) for women without a uterus and combined estrogen progestogen therapy (EPT) for women with an intact uterus.

ET prevents and treats postmenopausal osteoporosis. ET or EPT should be initiated around the time of menopause to achieve maximum bone protection. In the absence of contraindications, MHT (ET/EPT) initiated within 10 years of the last menstrual period or in women <60 years old is an effective treatment for moderate-to-severe vasomotor symptoms and genitourinary syndrome of the menopause (GSM).

Both ET and EPT have been shown to:

- Increase BMD at all skeletal sites in early and late postmenopause[115] **[Grade A, Level 1++]**
- Reduce fragility fracture risks (spine, hip and non-vertebral sites) by 20-35%[116,117] **[Grade A, Level 1+]**
- Statistically reduce hip fracture incidence by 33%, in the Women's Health Initiative study, with six fewer fractures per 10,000 person-years overall[116,118] **[Grade A, Level 1+]**

The effect of estrogen on bone is dose-related[117,118] **[Grade A, Level1+]**

- Standard-dose ET and EPT reduces postmenopausal osteoporotic fractures (spine, hip, and non-vertebral sites) even in women without osteoporosis[117,118] **[Grade A, Level1+]**
- Low dose MHT has been shown to protect bone by decreasing bone turnover markers (BTM) and preventing bone loss. However, data on the efficacy of low dose MHT on fracture efficacy is not robust[119,120] **[Grade B, Level 2++]**
- Discontinuation of MHT results in accelerated bone turnover, decrease in BMD and loss of anti-fracture efficacy[121] **[Grade D, Level 3]**[122] **[Grade B, Level 2++]**

The risks of MHT vary with dose, duration, route of administration, timing of initiation and the type of estrogen or progestogen used. Oral estradiol has a lower risk for venous thromboembolism (VTE) than conjugated equine estrogen (CEE) (Relative Risk [RR] 0.85, CI, 0.76 – 0.95).[123] **[Grade C, Level 2+]**

Transdermal estrogen (either as a gel, patch, or spray) compared to oral estrogen, has been found to be as effective in preserving bone density, and is more favourable to the cardiovascular (CV) system, less thrombogenic and associated with a lower risk of thromboembolism.[123] **[Grade C, Level 2+]**[124,125] **[Grade B, Level 2++]**

The addition of micronised progesterone or dydrogesterone in combined EPT preparations compared to other progestogens has been found to be associated with lower risk for CV, thromboembolic and breast cancer events.[126,127] **[Grade A, Level 1++]**

MHT utilisation in women <60 years old or within 10 years of menopause has not been shown to increase the risk of CV events, stroke, VTE and haemorrhagic stroke.[128] **[Grade A, Level 1++]**

However, initiation of MHT in women >60 years old or after 10 years of menopause for the prevention of osteoporosis fractures is not recommended.[128] **[Grade A, Level 1++]**

A full gynaecological assessment is mandatory prior to starting MHT with the dose and type of MHT tailor-made for that individual.[129] **[Grade A, Level 1++]**

- There is presently no definite duration for MHT use
- An annual medical review is advised with a risk- benefit evaluation leading to a shared decision to either continue, taper, or stop MHT

Premature Ovarian Insufficiency (POI) occurs when the ovaries stop functioning before the age of 40 years. Women with POI require hormones in view of the increased risk of osteoporosis, CV disease, and urogenital symptoms. Unless contraindicated, MHT or oral contraceptives (which are less effective than MHT for bone health) is advised until the average age of menopause, when treatment may be reassessed.[128] **[Grade A, Level 1++]**

5.5 Tibolone

Recommendation

- Women who are one year past their last period may be offered Tibolone for the relief of menopausal symptoms and prevention of osteoporosis — ***Grade A***

Tibolone is a synthetic hormone with estrogenic, progestogenic, and androgenic properties and is indicated for the relief of menopausal symptoms and the prevention of osteoporosis in postmenopausal women.[130] **[Grade A, Level 1++]**[131] **[Grade A, Level 1+]**

Efficacy of tibolone

The Long-term Intervention on Fractures with Tibolone (LIFT) study,[132] **[Grade A, Level 1++]**[133] **[Grade A, Level 1+]** involved postmenopausal osteoporotic women between 60-85 years old and non-osteoporotic women and compared 1.25 mg and 2.5 mg tibolone with placebo. 1.25 mg tibolone significantly increased lumbar and hip BMD, and greater absolute reduction among women with prior vertebral fracture (20.8 per 1000 person-years) than with no prior vertebral fracture (8.6 per 1000 person-years).[132] **[Grade A, Level 1+]**

Safety of tibolone

Tibolone is not advised in older postmenopausal women due to increased risk of stroke and in women who have strong risk factors for stroke, such as hypertension, smoking, diabetes, and atrial fibrillation.[132] **[Grade A, Level 1+]**

Tibolone is not associated with increased risk of coronary events or VTE,[123] **[Grade B, Level 2+]**[134] **[Grade A, Level1++]** or increased mammographic breast density.[135] **[Grade A, Level1++]**[136] **[Grade B, Level 2+]**[133] **[Grade A, Level 1+]** Although tibolone is not associated with an increased risk of breast cancer,[135] **[Grade A, Level1+]**[136] **[Grade B, Level 2+]**[133] **[Grade A, Level 1+]** it is not recommended in breast cancer survivors due to an increased risk of recurrence.

Monitoring

Women on tibolone should be monitored annually similar to women on MHT.[129,137] **[Grade A, Level 1+]**

5.6 Selective Estrogen Receptor Modulators

Recommendation

- Raloxifene may be recommended for postmenopausal osteoporosis as it reduces new vertebral fractures in women with or without prior fractures — ***Grade A***

SERM are synthetic non-steroidal molecules that bind to estrogen receptors throughout the body. They act as an estrogen agonist or antagonist depending on the target organ. Raloxifene (RLX) is a second-generation SERM.

Efficacy of raloxifene

Outcomes from the multicentre randomised placebo-controlled, double-blind Multiple Outcomes of Raloxifen Evaluation (MORE) study,[138,139] **[Grade A, Level 1+]** demonstrated that RLX increased BMD by 2-3% at the lumbar spine and femoral neck and reduced incidence of vertebral fracture by 40-50% after three years.

There was also a 22% decreased incidence of major osteoporotic fractures in women with prevalent vertebral fractures[140] **[Grade A, Level1+]** but no effect was seen on the risk of non-vertebral fractures. A 66% reduction in the incidence of invasive breast cancer and 76% reduction in the incidence of estrogen receptor (ER) positive invasive breast cancer was also seen.

Safety of raloxifene

RLX is associated with a 3-fold increase in VTE.[141] **[Grade A, Level 1+]** However, no cases of VTE were reported amongst healthy postmenopausal Asian women on RLX.[142] **[Grade C, Level 2+]** Other side effects include hot flushes, leg cramps and peripheral oedema.

5.7 Bisphosphonates

Recommendations

• Bisphosphonates are effective treatments for osteoporosis. The overall risk-benefit ratio of treatment with bisphosphonates for osteoporosis is positive	***Grade A***
• Oral bisphosphonates are not recommended for patients with an eGFR <30 ml/min (chronic kidney disease stage 4-5)	***Grade D*** ☑
• Zoledronic acid is contraindicated in patients with eGFR <35 ml/min	***Grade A***
• It is recommended to review the efficacy of bisphosphonate treatment after 3-5 years. Continuation of treatment would depend on the treatment response, occurrence of side effects, and future fracture risk	***Grade D*** ☑

Bisphosphonates are potent inhibitors of bone resorption.

5.7.1 Alendronate

[Grade A, Level 1++]

Alendronate at 10 mg daily for three years increases lumbar spine BMD by up to 8.8% and femoral neck BMD by 5.9% compared to placebo.[143] Vertebral and hip fractures are reduced by 50% in women with[143] or without[144] prior fracture. Wrist fracture is reduced by 50% in patients with prior vertebral fracture.[145] Fracture reduction is seen after one year of treatment.[146] Pooled analysis found an overall reduction in risk of hip fracture of 45% to 55% in patients receiving alendronate therapy.[147] Alendronate 70 mg weekly has similar efficacy to alendronate 10 mg daily in the treatment of postmenopausal osteoporosis.[146] Continuous use of alendronate, for up to 10 years, if clinically indicated,[148,149] produces a sustained increase in BMD and a 55% significant reduction in spine fracture with a good safety profile.

5.7.2 Risedronate

[Grade A, Level 1++]

Treatment with risedronate 5 mg daily for three years increases lumbar spine BMD by 6.4%[150] and femoral neck BMD by 3.4%[151] compared to placebo, and is associated with up to 49% reduction in new vertebral fracture in women with prior vertebral fractures,[152] and 39% reduction in non-vertebral fractures.[153] Vertebral fracture risk reduction is seen after six months of therapy.[154] Reduction of hip fracture risk after three years was 40% in women with confirmed osteoporosis and 60% in women with at least one co-existing vertebral fracture.[151]

Treatment with risedronate in the 4th and 5th year significantly reduced risk of new vertebral fractures by 59% compared to 49% in the first three years.[155] The mean increase from baseline in lumbar spine BMD over five years was 9.3%.[155] Currently, the use of risedronate for up to seven years, is safe and efficacious.[156] Risedronate 35 mg once weekly has similar efficacy to the 5 mg daily dosing.[154]

5.7.3 Ibandronate

[Grade A, Level 1+]

Treatment with oral ibandronate 150 mg/month increases the lumbar spine BMD by 6.6% over two years in postmenopausal osteoporotic women without prior fracture compared to placebo.[157] Oral ibandronate 2.5 mg daily for three years reduces vertebral fracture by 62% in postmenopausal women with prevalent vertebral fracture.[158]

Ibandronate 150 mg/month has been shown to be non-inferior to the 2.5 mg daily dose in terms of BMD gain and incidence of vertebral fracture.[159] Ibandronate 150 mg/month significantly reduced non-vertebral fracture by 38-43% over two years – based on pooled analysis of individual patient data.[160]

5.7.4 Zoledronic acid

[Grade A, Level 1++]

Treatment with zoledronic acid (ZA) (5 mg intravenous [IV] infusion over at least 15 minutes once yearly) in osteoporotic postmenopausal women over three years[161] reduces incidence of vertebral fractures by 70% with significant reduction seen by one-year, hip fracture by 41%, and non-vertebral fracture by 25%. ZA yearly infusion also[162] reduced the risk of new clinical fractures by 35% in patients who recently (within 90 days) had a low trauma hip fracture and was associated with reduction in mortality of up to 28% in the same trial. At three years, patients on ZA will require re-evaluation[163-165] as continuing therapy with ZA beyond three years only provided marginal benefit, as shown in the Phase III trial extended up to six years and nine years.[163,164]

Treatment with IV ZA provides an alternative osteoporosis treatment to patients who cannot tolerate oral bisphosphonates including those who cannot swallow or sit up straight, and who have had bariatric procedures.

ZA may cause flu like symptoms (e.g. pyrexia and myalgia) that may last 1-7 days, particularly after the first dose.[51] This can be minimised by pre-treatment with paracetamol or ibuprofen, and administering ZA over 30 minutes or longer. Baseline measurements taken before ZA infusions should include renal function, serum calcium and serum 25-hydroxyvitamin D [25(OH)D]. ZA is not recommended in patients with an eGFR below 35ml/min/m^3.[51,166] Hypocalcaemia may occur after ZA particularly in those with vitamin D deficiency.[167] It is recommended that in the ideal setting, serum 25(OH) D levels should be evaluated and corrected to at least ≥ 50nmol/L prior to ZA infusion to prevent hypocalcaemia.[168]

5.7.5 Complications of bisphosphonate therapy

Atypical femoral fractures (AFFs)

AFFs have been increasingly recognised as potential complications of bisphosphonate therapy.[169] The risk of AFFs increases with duration of bisphosphonate use.[170] The age-adjusted incidence rate of AFFs has been estimated to be 1.78 per 100,000 person-years in patients on bisphosphonate use <2 years and the incident rate increases to 113.1 per 100,000 person-years with >8 years' duration.[171]

Though it has been shown that Asians on bisphosphonate therapy may have an increased risk of AFFs compared to Caucasians,[172,173] AFFs have also been found to occur in patients without a history of bisphosphonate therapy.[174] Patients on anti-resorptive therapy who develop thigh pain should have imaging performed to look for evidence of stress changes in the femur within the AFF spectrum.[170] Overall, the benefit of reducing further osteoporotic fractures with bisphosphonate treatment is much greater than the small absolute risk of AFFs.[169,172,175]

Management of AFFs[169]

- Discontinue anti-resorptives
- Ensure adequate calcium and vitamin D intake, with supplementation, as required
- Trial of conservative management in those with incomplete AFFs without pain
  - If there are no symptomatic and radiographic improvement after 2-3 months, prophylactic nail fixation should be strongly considered, because these patients may progress to a complete fracture
- Surgical management with intramedullary nail fixation is recommended for incomplete AFFs with pain, and complete AFFs
  - After surgical treatment of AFFs, further medical treatment has to balance the risk of causing new atypical fractures against the risk of fragility fractures when not treating osteoporosis
  - Even though observational data suggest that teriparatide (recombinant human parathyroid hormone 1-34 [r-PTH]) might result in faster healing of surgically treated AFFs, the European Calcified Tissue Society guidelines do not recommend r-PTH for AFF healing apart from reducing the risk of typical fragility fractures.[176] However, in patients at high risk of further osteoporotic fractures, a course of r-PTH for two years is recommended. Following the 2-year course of r-PTH, further treatment needs to be given to maintain the r-PTH BMD gain
- Other treatment options would depend on the risk level of further fragility fractures (high/low) and/or whether the AFFs have been treated non-operatively or surgically managed[176]
- Assess the contralateral hip for possible asymptomatic AFF

Osteonecrosis of the jaw (ONJ)

ONJ is defined as “exposed”, non-vital bone involving maxillofacial structures with delayed healing despite >8 weeks of appropriate medical care.[177] ONJ is usually associated with invasive dental procedures thought to be caused by trauma to dentoalveolar structures with limited capacity for bone healing but, can also occur de novo.[178]

The absolute risk of ONJ is very low ranging from 1 in 10,000 to 1 in 100,000.[179] However, the risk of ONJ reaches 21 in 10000 (0.21%) in patients on >4 years of oral bisphosphonates.[173] ONJ is likely to occur earlier in those treated with IV versus oral forms of bisphosphonates[180] and those on longer duration of therapy.[181] It is more commonly seen (incidence rates from 4-13%) in patients on oncological doses (high dose and more frequent IV) of bisphosphonates and denosumab including those[182] on cancer treatment, with bone metastasis, who are immune suppressed, have had radiation, on anti-angiogenic therapies, with infection, poor oral hygiene and, have had invasive dental procedures.

ONJ may be managed conservatively at stage 0-2, but surgical debridement and resection is recommended for stage 3 ONJ (see Appendix 5 for detailed description and treatment of ONJ stages).[183] There are no recommendations to stopping bisphosphonates for dental procedures but initiation should be deferred until the area is healed.[184]

Other side effects of bisphosphonates

Other common side effects of oral bisphosphonates are gastrointestinal, commonly nausea, although actual incidence is low.[185,186] Proper administration of bisphosphonates by taking it in the morning on an empty stomach, 30 minutes before food with a glass of water, in an upright position, will improve the systemic absorption of the drug and reduce the small risk of oesophagitis and oesophageal ulceration. The evidence to date on the association of oral bisphosphonates and oesophageal cancer from the United Kingdom General Practice Database remains inconclusive. For patients with upper gastrointestinal disease, IV ZA or denosumab are alternatives. Some generic forms of alendronate are more poorly tolerated in terms of gastrointestinal side effects, leading to poor adherence.[187]

There has been some concern over the association of bisphosphonates to atrial fibrillation, but results have been conflicting.[188] There is a reported increased risk of cardiac arrhythmias in patients who continued ZA for nine years versus those who discontinued at six years.[164] A meta-analysis from randomised controlled trials and observational studies suggested a significantly increased risk of atrial fibrillation requiring hospitalisation, but no increase in the risk of CV mortality, with the use of bisphosphonate.[189] To date, there has not been an association between bisphosphonate with strokes.[189]

5.7.6 Use of bisphosphonates in renal impairment and chronic kidney disease

In patients with chronic kidney disease without evidence of CKD-MBD (chronic kidney disease-mineral bone disease), the use of bisphosphonates for fracture risk reduction should not differ from general population guidelines.[190] **[Grade A, Level 1+]**

Post hoc analyses of pivotal clinical trials evaluating bisphosphonates found that they had similar efficacy, improved BMD and reduced fractures, in subjects with mild or moderately reduced eGFR (up to CKD stage 4 [see Appendix 6 for CKD stages]) compared to those with normal eGFR.[191] **[Level 1+]**

In those at CKD stage 3b-4, bisphosphonate users had a 14% higher risk of CKD stage progression than non-users.[192] **[Level 2+]**

Oral bisphosphonates are not recommended for patients with an estimated GFR <30 ml/min (stage 4-5). **[Grade D, Level 4]** The IV bisphosphonate, ZA, is contraindicated in patients with an eGFR <35mL/min.[193] **[Grade A, Level 1+]**

5.7.7 Long-term use of bisphosphonates

It is recommended that after five years of oral bisphosphonates or three years of IV bisphosphonates, there should be a reassessment of the patient's fracture risk.

Table 5-1. Recommended duration of bisphosphonate therapy for women

Risk stratification	Recommended duration of treatment
Women at high-risk, e.g. • Fracture during treatment • Low hip T-score ≤2.5 • High fracture risk score with FRAX® • Previous major osteoporotic fracture • Older women >70-years-old with any of the above risk factors	• Continue for up to 10 years (oral) or 6 years (IV) with periodic evaluation[194] **[Grade D, Level 4, ☑]**
Women not at high-risk	• After 3-5 years of bisphosphonates therapy, a drug holiday of 2 years can be considered[194] **[Grade D, Level 4, ☑]**[195] **[Level 2+]**

However, it has been shown that there is an increased risk of hip and vertebral fractures after a 2-year drug holiday for those on the oral bisphosphonates, alendronate and risedronate,[195] **[Level 2+]** which would suggest that patients should be reviewed no longer than two years after starting a drug holiday.

5.8 Recombinant human PTH 1-34

Recommendations

- r-PTH/teriparatide is indicated for individuals with very high risk for fractures or osteoporosis not responding to treatment — ***Grade A***
- r-PTH therapy is recommended for up to 24 months — ***Grade B***

Recombinant human PTH 1-34 (r-PTH/teriparatide), is a potent anabolic agent. r-PTH is indicated for individuals at very high risk for fractures (e.g. those with multiple vertebral fractures) or osteoporosis not responsive to other anti-osteoporosis therapy (see also Section 5.13 Treatment failure).[111,196] **[Grade A, Level 1++]**

Subcutaneously administered r-PTH at 20 µg daily for 21 months increases lumbar spine BMD by up to 8.6% and femoral neck BMD by 3.5% compared to placebo in postmenopausal women with vertebral fractures.[109]

A meta-analysis comparing r-PTH with placebo showed a 74% reduction in risk of vertebral fractures (HR, 0.26; 95% CI, 0.18 to 0.39) and a 39% reduction in the risk of non-vertebral fractures (HR, 0.61; 95% CI, 0.44 to 0.85).[111] **[Grade A, Level 1++]** A head-to-head comparison[114] **[Level 1++]** between r-PTH (anabolic) and risedronate (anti-resorptive) [VERO Trial] in postmenopausal women at very high risk of fracture, showed superiority of r-PTH in vertebral and clinical (non-vertebral plus clinical vertebral) fractures.

Current recommendation for the treatment duration of r-PTH is up to 24 months. **[Grade B, Level 1+]** The benefits of anabolic therapy wear off within one year of discontinuation,[197] **[Grade B, Level 1+]** hence, the recommendation is to initiate anti-resorptive therapies, when stopping anabolic therapy, to maintain bone density gains.[198,199] **[Grade A, Level 1++]**[200] **[Grade B, Level 1+]**

Side effects include dizziness, leg cramps and hypercalcaemia. Serum calcium should be checked prior to starting r-PTH. The drug is contraindicated in patients with open epiphyses (children and adolescents), Paget's disease of the bone, prior radiation therapy involving the skeleton, bone malignancies, metabolic bone diseases other than osteoporosis or pre-existing hypercalcaemia. **[Grade D, Level 4, ☑]**

5.9 Denosumab

Recommendations

• Denosumab is an effective anti-resorptive treatment for osteoporosis especially for those at high risk of osteoporotic fractures	***Grade A***
• A denosumab 'drug holiday' is not recommended due to an associated rebound increase in bone turnover and increased risk of multiple vertebral fractures (especially in those at high risk of osteoporotic fractures) when the drug is discontinued	***Grade B***
• Treatment reassessment may be done after 5-10 years and those who remain at high fracture risk should either continue denosumab or be switched to other osteoporosis therapies	***Grade D ☑***
• If denosumab is stopped, subsequent treatment with another treatment option should be initiated to prevent the rebound increase in bone turnover seen with denosumab withdrawal	***Grade D ☑***

Denosumab is a human monoclonal antibody (IgG) that inhibits the formation, function, and survival of osteoclasts by inhibiting RANK (receptor activator of nuclear factor kappa-B) ligand, thus reducing bone resorption.[201]

Efficacy of denosumab

The FREEDOM trial (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) – 6-monthly subcutaneous denosumab 60 mg over three years vs placebo[202] **[Level 1++]** demonstrated significant increase in BMD (9.2% for lumbar spine, 60% for total hip, 4.8% in femoral neck and 3.5% in distal 1/3rd radius) and significantly reduced the relative risk of new fractures by 68% (vertebral), 40% (hip) and 20% (non-vertebral). In the open-label extension trial (denosumab for up to 10 years),[203] **[Level 1++]** there was continued improvements in BMD with increases from baseline after three years. The yearly incidences of new vertebral and non-vertebral fractures were similar to that observed at three years.

Denosumab has also demonstrated greater BMD gains after 12 months of treatment with denosumab vs ZA at all skeletal sites in postmenopausal women switched from oral bisphosphonates to injectables.[204] **[Level 1+]**

Discontinuation of denosumab

Although a potent anti-resorptive, discontinuation of denosumab is associated with a rebound increased in bone turnover, loss of BMD and possible increased risk of multiple vertebral fractures especially in the high-risk group.[205] **[Level 2+]**

A placebo controlled randomised controlled trial showed that four doses of denosumab given 6-monthly significantly increased BMD and reduced bone turnover, however, on stopping denosumab, the BTM serum carboxy-terminal collagen crosslinks (CTX) and procollagen type 1 N-terminal propeptide (P1NP) increased to above baseline levels as early as 3-6 months and returned to baseline by 24 months.[206] **[Level 1+]** BMD at all sites decreased within 12-24 months, and spine and total hip BMD reached baseline at 12 months. Significant BMD loss occurred despite longer treatment duration.[207] **[Level 4]**[208] **[Level 2+]**

Participants who discontinued denosumab during the FREEDOM trial and its extension,[209] **[Level 2++]** had increased rates of new vertebral fractures similar to those on placebo. Of those who experienced at least one vertebral fracture, 60.7% had multiple fractures. The risk of developing vertebral fractures post-denosumab cessation were individuals with history of vertebral fractures.

Missing or delaying denosumab doses by a few months may result in an elevated risk of vertebral fractures and should be avoided.[209] **[Level 2++]** Hence the concept of drug holiday is not applicable to denosumab.

Those who have stopped denosumab should be transitioned to other treatments for osteoporosis to reduce the rebound increase in bone turnover and fracture risk associated with denosumab withdrawal.[208] **[Level 2+]**[205] **[Level 4]**

Adverse events

Over 10 years of treatment showed a consistent safety profile with low incidence of adverse events such as serious infections, cellulitis, hypocalcaemia, eczema and malignancy.[203] **[Level 1++]** There was also low cumulative exposure-adjusted incidence of AFFs (0.8 per 10000 participants-years) and ONJ (5.2 per 10000 participant-years).[203] **[Level 1++]**

Denosumab and renal impairment

Treatment with denosumab resulted in significant BMD increases at all sites in CKD stages 1-3 (eGFR >30ml/min) and the hip in CKD stage 4 (eGFR 15-29ml/min). It also reduced vertebral and non-vertebral fracture rates in CKD stages 1-3.[210] **[Level 2++]** There is a greater risk of hypocalcaemia in patients with CKD especially those with eGFR<30ml/min or on dialysis.[211] **[Level 2+]** It is important to ensure adequate calcium and vitamin D intake before commencing denosumab in those at risk of hypocalcaemia.[211] **[Level 2+]**

5.10 Romosozumab

Recommendations

• Romosozumab is an anabolic agent for the treatment of osteoporosis especially in patients with a very high fracture risk; preferably in those with low CV risk	***Grade A***
• Treatment with romosozumab is for 12 months, followed by anti-resorptive therapy, e.g. denosumab or bisphosphonate	***Grade A***
• Romosozumab is currently not recommended in patients with a history of a CV event within the past one-year, and should be used cautiously in patients with high CV risk and only when benefits outweigh risks	***Grade B***

Romosozumab (RMZ) is an anabolic agent. It is a humanised monoclonal antibody that binds to sclerostin. Changes in BTM point to a dual effect on bone remodelling, with a transient increase in formation markers and reduction in resorption, resulting in an increase in bone formation and BMD.

RMZ has been shown to exhibit a dose-dependent increase in BMD at the spine and hip in all the Phase III trials.[110,212-214] **[Level 1++]** The increase is seen as early as six months after RMZ initiation and has demonstrated similar outcomes in both men[214] **[Level 1++]** and women.[110,212,213] **[Level 1++]**

In the placebo-controlled FRAME trial involving women with postmenopausal osteoporosis,[212] **[Level 1++]** RMZ significantly increased BMD in 12 months and reduced new vertebral fractures and clinical fractures by 73% and 36%, respectively. In the second year,[212] **[Level 1++]** the cumulative 24-month incidence of new vertebral fractures was significantly reduced in the RMZ/denosumab than in the placebo/denosumab group by 75% and 33%, respectively.

The ARCH trial,[110] **[Level 1++]** a randomised controlled study with an active bisphosphonate comparator group demonstrated superiority of RMZ over alendronate at both 12 (double-blind) and 24 months (both groups on open-label alendronate). Over 24 months there were significant reductions in vertebral fractures (48%), clinical fractures (27%) and hip fractures (38%) in the RMZ/alendronate group compared to the alendronate/alendronate group.

Compared to r-PTH, RMZ led to a larger anabolic window and showed greater gains in BMD and bone strength when assessed by finite element analysis.[213] **[Level 1++]**

Adverse events

The ARCH trial found a numerical imbalance in adjudicated major adverse cardiac events (MACE) with more events (cardiac ischaemic events and cerebrovascular events) occurring in subjects randomised to RMZ compared to alendronate. In total (of three major randomised Phase III trials with RMZ),[110,212,214] **[Level 1++]** 1.3% (n=77) in the RMZ arms and 0.9% (n=53) in the control arms experienced a MACE (Hazard Ratio [HR], 1.40; 95% CI, 0.99 to 1.99).[215] In Malaysia, RMZ is contraindicated in patients who have had a myocardial infarction or stroke within the past one year.

5.11 Calcium and Vitamin D

Recommendation

- Vitamin D supplementation (at least 800 IU/day) in combination with calcium (1200 mg/day elemental calcium) is recommended for fracture and fall prevention in people above 50 years of age who are at risk of fractures, particularly when initiating active osteoporosis therapies — ***Grade A***

Although population-level intervention has not been shown to be an effective public health strategy,[216] calcium and vitamin D supplementation may lead to a modest reduction in fracture risk.[56]

The majority of medications for osteoporosis treatment are licensed in the context of calcium and vitamin D repletion. The evidence supports that calcium combined with a vitamin D supplement be prescribed in the treatment of osteoporosis in people of ≥50 years old.[217] **[Level 1-]** Table 5-2 lists the percentage of calcium absorption from different types of formulation and Table 5-3 describes the evidence for calcium, vitamin D and their combination.

The evidence supports calcium combined with a vitamin D supplement, in the treatment of osteoporosis in people ≥50 years old at doses of 1200 mg/day of calcium and 800 IU/day of vitamin D to achieve maximum therapeutic effect[218-221] **[Level 1++]**

Table 5-2. Ranges of calcium absorption from different sources[222]

Type	Elemental calcium (%)	Average calcium absorption (%) (Range)
Calcium carbonate	40	26 (13.8-64)
Calcium citrate	21	22 (12.3-31.4)
Calcium lactate	13	32
Calcium gluconate	9	34 (21-8-67.5)
Milk (non-calcium enriched)	33	33 (21.4-37.7)

Table 5-3. Evidence for managing osteoporosis using calcium and Vitamin D

Calcium	• Based on a systematic review and meta-analysis, calcium has a small benefit for total fracture risk but not for vertebral or hip fractures[223,224] **[Level 1++]** • A 2015 meta-analysis reported that in 26 randomised controlled trials, calcium supplements reduced the risk of total fracture (20 studies, n=58,573) with a RR 0.89, (95% CI 0.81, 0.96), reduced the risk of vertebral fracture (12 studies, n=48967) with a RR of 0.86 (95% CI 0.74, 1.00) and had no effect on hip or forearm fractures (13 studies, n=56,648; RR 0.95, 95% CI 0.76,1.18 and 8 studies, n=51775; RR 0.96, 95% CI 0.85,1.09, respectively[225] **[Level 1++]**

Calcium with vitamin D	• A meta-analysis showed that calcium and vitamin D led to a modest reduction in fracture risk especially those at highest risk of calcium and/or vitamin D deficiency[226] **[Level 1++]** • Among institutionalised and community dwelling older adults, calcium plus vitamin D supplementation significantly reduced risk of total fractures by 15% (summary relative risk estimate [SRRE] 0.85, 95% CI 0.73,0.98) and hip fractures by 30% (SRRE 0.70, 95% CI 0.56, 0.87)[56] **[Level 1++]**
Vitamin D	• Adequate levels could reduce falls in the elderly which indirectly influences the risk of fracture. Its effect was through improvement of muscle strength, gait, and balance[221] **[Level 1+]**

Safety of calcium and Vitamin D supplementation

Calcium supplements are associated with gastrointestinal side-effects, and a small increased risk of renal stones. There is inadequate evidence that calcium and/or vitamin D supplementation increases cardiovascular risk.[217]

5.12 Activated Vitamin D

The available activated vitamin D analogues are calcitriol and alfacalcidol. Calcitriol (0.25 µg bd) has been demonstrated to increase BMD in those with postmenopausal osteoporosis[227] and reduce vertebral fractures.[228] **[Level 1+]** Alfacalcidol (1 µg od) has been shown to increase BMD in those with postmenopausal osteoporosis[229,230] **[Level 1+]** and was effective in reducing the incidence of hip fractures in older people with and without pre-existing osteoporotic fractures.[231] **[Level 1++]**

In a comparative meta-analysis, combining the activated vitamin D analogues (alfacalcidol and calcitriol) were found to be superior to native vitamin D with regard to effects on lumbar spine bone loss and spinal fracture rates in primary osteoporosis.[232] **[Level 1++]**

In a network meta-analysis of 13 randomised controlled trials, which included patients with postmenopausal osteoporosis and those on glucocorticoids, results indicate that combining treatment with alendronate and alfacalcidol was significantly better in preventing bone fractures than alendronate alone (OR=0.53, 95% CI: 0.19-0.95) and alfacalcidol alone (Odds ratio [OR]=0.25, 95% CI: 0.08- 0.49).[233] **[Level 1+]**

A retrospective study in Japanese postmenopausal women comparing denosumab + vitamin D and denosumab + alfacalcidol showed a greater gain in femoral neck and distal forearm BMD compared to those on plain vitamin D.[234] **[Level 3]**

Hypercalciuria and hypercalcaemia may complicate therapy with active vitamin D analogues. All patients on activated Vitamin D should avoid taking more than 500 mg of calcium supplements daily to reduce the risk of hypercalcaemia and renal stone disease. Serum calcium should be monitored periodically, at minimum before starting therapy, and at 3- to 6-monthly intervals thereafter.[235] In addition, measurement of 24-hour urinary calcium can be considered in those on calcitriol, especially in those with renal impairment.[236]

However, most of the trials with activated vitamin D analogues involved a small number of subjects and were of relatively short duration. This limited evidence precludes the inclusion of activated vitamin D analogues in the routine management of postmenopausal osteoporosis. We suggest that activated vitamin D analogues can be considered when patients are risk of fracture are unable to tolerate other recommended active osteoporosis therapies, i.e. SERMs, bisphosphonates, denosumab, teriparatide, romosuzomab, or if these therapies are unavailable. **[Grade D, Level 4]**

5.13 Treatment failure

Recommendations

• Treatment failure can be considered when two or more osteoporotic fractures occur and/or <25% change in bone turnover markers and/or worsening BMD during treatment	***Grade C***
• Before considering treatment changes, patients need to be assessed for treatment adherence, and for the possibility of secondary osteoporosis	***Grade B***

The aim of osteoporosis treatment is to minimise fracture risk. The available anti-osteoporosis medication has been shown to reduce fracture risk by 40-70% but do not eliminate the risk. Patients who are on osteoporosis therapy may still develop fractures and this may reflect 'residual disease'.

Treatment failure may be considered with the occurrence of,[49] **[Grade C, Level 4]**

- ≥2 osteoporotic fractures occurring during treatment
- when serial measurements of bone remodelling markers,
  - <25% reduction from baseline after six months for anti-resorptive therapy
  - <25% increase after six months for anabolic therapy
- where BMD continues to decrease
  - ≥5% in at least two serial BMD measurements at the lumbar spine or 4% at the proximal femur

Before concluding that a treatment has failed, the following factors listed in Table 5-4 should be addressed, as these factors may account for the undesirable outcome as mentioned.

Table 5-4. Factors that should be addressed before concluding treatment failure

Duration of treatment[237] [Grade C]	• The change in BMD occurs with at least 12 months of treatment with most osteoporosis therapy. If the fracture occurs within the first treatment year, there is no reason to change therapy
Adherence to therapy[238,239] [Level 2++][240] [Level 1-]	• The adherence to osteoporosis therapy is suboptimal with adherence rates ranging between 12.9-94%, which reduces notably over time • Poor medication adherence is associated with increased fracture rate by 30% at any skeletal site • Adherence should be evaluated at each clinic visit or through the dedicated fracture liaison service
Existing secondary osteoporosis or inter-current condition which increases bone resorption[241,242] [Grade C]	• Up to 32-50% of patients with osteoporosis have secondary causes • Response to anti-osteoporosis medication may be limited if the underlying disease is undiagnosed or poorly controlled
Vitamin D deficiency[243-245] [Level 2+]	• Vitamin D deficiency accelerates bone loss and can lead to osteomalacia, muscle weakness and secondary hyperparathyroidism

The following recommendations for switching anti-osteoporosis medication could be considered if the initial treatment has failed.[49] **[Level 4]**

1. A weaker anti-resorptive to be replaced by a more potent drug of the same class, e.g. alendronate in preference to ibandronate
2. An oral drug to be replaced by an injected drug, e.g. ZA or denosumab in preference to alendronate
3. A strong anti-resorptive is reasonably replaceable by an anabolic agent (or dual action therapy), e.g. r-PTH/teriparatide or romosozumab in preference to denosumab

In patients with severe osteoporosis with multiple osteoporotic fractures, a more potent agent should be initiated and an anabolic agent should be preferred to minimise subsequent fractures and treatment failure. To date, combination anabolic/anti-resorptive therapy is not recommended until its effect on fracture risk is better understood.[13,246] The most promising combination therapy tested is the concomitant use of r-PTH/teriparatide and denosumab as reported in the DATA study.[247,248] **[Grade A, Level 1++]** A total of 94 postmenopausal women with osteoporosis were randomised to receive either teriparatide, denosumab, or both medications for 24 months. Compared to a single drug, the combination therapy reported a higher increase in spine and hip BMD, especially apparent in the first 12 months of treatment.

SECTION 6:
SURGICAL MANAGEMENT OF OSTEOPOROTIC FRACTURES

Recommendations

• Osteoporotic hip fractures are best treated by early (<48 hours) surgical intervention	***Grade B***
• Osteoporotic vertebral fractures can be initially treated conservatively; vertebral augmentation procedures can be considered in specific circumstances if conservative treatment fails	***Grade A***
• Following surgical treatment for osteoporotic fractures, all patients should receive active management for osteoporosis	***Grade A***

Surgical treatment goals in osteoporotic fractures are early weight bearing/ mobilisation and a return to normal activities.

Osteoporotic hip fractures are best treated by early (<48 hours) surgical intervention.[249] **[Level 2+]** When there is an operative delay of >48 hours, a meta-analysis found that the odds ratio for 30-day mortality was 1.41 (95% CI = 1.29-1.54, P < 0.001), and that for one-year mortality was 1.32 (95% CI = 1.21-1.43, P < 0.001).[250] **[Level 2++]** Non-operative management is discouraged as it places the patient at risk of complications due to immobility (e.g. respiratory problems, thromboembolic disease, pressure ulcers, further bone loss) and mortality.[251,252] Intracapsular hip fractures are treated with a total hip replacement or arthroplasty; trochanteric fractures above and including the lesser trochanter can be treated using a sliding hip screw in preference to an intramedullary nail; subtrochanteric fractures are treated with an intramedullary nail.[253]

Vertebral compression fractures are associated with increased morbidity and mortality.[254] However, most osteoporotic vertebral fractures are stable.

The initial management of an acute vertebral fracture include pain control and activity modification. Oral analgesics (e.g. non-steroidal anti-inflammatory drugs [NSAIDs]) are usually the first option for acute pain relief; if the pain does not improve after the initial treatment, mild opioids combined with paracetamol can be tried. For patients debilitated by pain, hospitalisation and parenteral analgesia may be necessary.

Patients should resume physical activity as quickly as possible. Complete bedrest is not recommended, as inactivity may result in further bone loss and deconditioning. Physical therapy is recommended for gait and core strengthening when the patient can tolerate this level of activity.[255] Exercise may improve mobility and reduce pain and fear of falling.[256] There is limited/low quality evidence on the efficacy of spinal orthoses for the treatment of osteoporotic vertebral compression fractures.[257,258]

For those patients who have persistent spinal pain and not settling on conservative treatment, operative vertebral augmentation intervention can be considered.[259] Other indications for vertebral surgery include vertebral fractures complicated by the spinal cord or nerve root compression, or progressive spinal deformities. **[Grade C, Level 4]**

The surgical options are as follows:

- Vertebroplasty, a percutaneous injection of cement augmentation of the vertebra has produced quick and significant relief of backache in selected cases.[260,261] **[Grade B, Level 3]** However, more recent guidelines have suggested that it has no demonstrable clinically significant benefit on pain, physical function and quality of life compared to placebo/sham procedure[256] **[Level 1++]**
- Balloon kyphoplasty is performed by inserting a balloon-like device in the fractured vertebrae which is inflated to increase the height of the vertebral body. However, there is insufficient evidence to support kyphoplasty over nonsurgical management or percutaneous vertebroplasty[256] **[Level 1++]**

All patients with osteoporotic fractures are at high risk for the development of further fractures. They should receive active management for osteoporosis (see Section 5) and advised regarding prevention of falls (see Section 4.3).

SECTION 7:

SECONDARY OSTEOPOROSIS

7.1 Glucocorticoid-induced osteoporosis (GIOP)

Recommendations

- All patients starting glucocorticoids and in whom it is anticipated that they will be continuing for more than three months should have an initial fracture risk assessment — ***Grade D*** ☑
- The presence of a previous fragility fracture, bone density measurement by dual-energy x-ray absorptiometry and the glucocorticoid-adjusted Fracture Risk Assessment Tool (FRAX®) scores are used to assess fracture risk in patients on glucocorticoids — ***Grade D*** ☑
- For patients on glucocorticoids with osteoporotic fractures, densitometric osteoporosis and/or very high fracture risk, oral bisphosphonates are the first line treatment — ***Grade A***

Osteoporosis is a major complication of glucocorticoid (GC) therapy. Patients on glucocorticoid therapy are at increased risk of sustaining fractures over and above that of the underlying disorder. **[Level 2+]**

Bone loss occurs most rapidly in the first 6-12 months of oral GC therapy,[262,263] and is more pronounced in trabecular bone, which is predominantly present in spine.[264] **[Level 1++]** There is an increase in fracture risk that appears within 3-6 months of starting GC.[263] **[Level 1++]**

Fractures occur in patients with GIOP at a higher bone mineral density measurement (BMD) compared to postmenopausal osteoporosis.[265] **[Level 2++]** Prednisolone ≥2.5 mg daily or its equivalent, for >3 months is associated with low BMD and fractures.[266] **[Level 1++]** A high daily dose of oral GC (≥15 mg) or a cumulative GC dose of ≥1 g has been found to be associated with a higher hip fracture risk.[267] **[Level 2++]** Standard doses of inhaled or topical GC use for a few years have not been shown to adversely affect BMD.[268,269] **[Level 1++]** However, inhaled high potency GC (>600-2000 mcg),[270,271]

total cumulative dose of inhaled GC[272] **[Level 1++]** and/or taken over an extended period time (>8 years)[271] have been associated with significant bone loss/fracture. **[Level 2+]**

7.1.1 Assessment of fracture risk and diagnosis

The use of BMD measurement for the diagnosis of GIOP is not crucial, but may be useful in the monitoring of therapy and as part of the fracture risk assessment tool. Assessment of fracture risk should be performed in all individuals committed or likely to receive oral GC for ≥3 months.[273] **[Grade D, Level 4]**

In the 2017 American College of Rheumatology guidelines for the prevention and treatment of GIOP, patients are divided into those aged below and above 40 years. Clinical risk factors and GC-adjusted Fracture Risk Assessment Tool (FRAX®) scores are used to categorise patients into low, medium and high-risk groups with respect to the 10-year risk of fracture.[274] The classification of low, medium and high fracture risk is shown in Table 7-1.

Table 7-1. The American College of Rheumatology classification of high, moderate and low fracture risk[274]

	High	Moderate	Low
Above 40 years *(Presence of any one of these features)*			
Prior fracture	+	-	-
Hip or spine BMD T-score ≤ -2.5 in men age >50 years and postmenopausal women	+	-	-
FRAX® (GC-adjusted): major osteoporotic fracture	≥ 20%	10-19%	< 10%
FRAX® (GC-adjusted): hip fracture	≥ 3%	>1 and <3%	≤ 1%

	High	Moderate	Low
Below 40 years	Prior osteoporotic fracture(s)	Hip or spine BMD Z-score < -3 or rapid bone loss ≥10% at the hip or spine over 1 year) **and** continuing GC treatment at ≥7.5 mg/day for ≥6 months	None of the above risk factors apart from GC treatment

Adapted from Buckley L, et al. Arthritis Care Res (Hoboken) 2017.[274]

Calculation of GC-adjusted FRAX® scores is shown in Table 7-2.

Table 7-2. Adjustments to FRAX® scores based on glucocorticoids exposure[275]

Dose	Prednisolone equivalent (mg/day)	Percentage adjustment
Hip fracture		
Low	<2.5 mg	-35%
High	>7.5 mg	+20%
Major osteoporotic fracture		
Low	<2.5 mg	-20%
High	>7.5 mg	+15%

For medium doses (2.5-7.5 mg daily), the unadjusted FRAX® value can be used.[275] However, FRAX® cannot be adjusted to account for the cumulative dosage or length of use.[276]

Patients with a low fracture risk can be monitored. Patients with a moderate or high fracture risk are recommended to start treatment depending on the age, gender and childbearing potential in females (see Algorithm B).

The National Osteoporosis Guideline Group suggests that in general, women age ≥70 years, or with a previous fragility fracture, or taking large doses of GC (≥7.5 mg/day of prednisolone or equivalent/day) exceed the intervention threshold and should be considered for bone protective therapy.[277] **[Grade D, Level 4]**

7.1.2 Management of GIOP

General measures [Grade D, Level 4, ☑]

- Prescribing the lowest effective dose of GC for disease control[278]
- Optimise treatment of the underlying disease[262]
- The use of alternative route of administration[278] (e.g. inhaled steroids in asthma)
- Consider the use of steroid-sparing agents
- Modification of lifestyle – adequate calcium and vitamin D intake, regular exercise, avoid smoking, limiting alcohol, and prevention of falls[274]

Specific measures

All patients on GC should be supplemented with calcium and vitamin D (1000-1200 mg/day and 800 IU/day respectively), with the aim to achieve a serum 25-hydroxy vitamin D [25(OH)D] level of ≥50 nmol/L (≥20 ng/mL).[274,279] **[Grade A, Level 1++]**

In hypogonadal states, replacement therapy with sex steroids should be considered.[280-282] **[Grade B, Level 2++]**

Drugs found to be effective in management of GIOP are shown in Table 7-3.

Table 7-3. Grades of recommendation for preventive and therapeutic interventions in GIOP

Drug	Primary prevention	Secondary prevention/ treatment	Vertebral fracture reduction	Hip fracture reduction
Alendronate[267,283-286]	A	A	A	B
Alfacalcidol[284,287-289]	A	A	ND	ND
Calcitriol[288,290]	A	A	ND	ND
Calcium & Vitamin D[279,291]	ND	A	ND	ND
Denosumab[284,292,293]	A	A	A	ND
Ibandronate[294,295]	A	ND	ND	ND
MHT (in females)[280,282]	ND	A	ND	ND
Pamidronate[296,297]	A	A	ND	ND

Drug	Primary prevention	Secondary prevention/ treatment	Vertebral fracture reduction	Hip fracture reduction
Raloxifene[298]	ND	A	ND	ND
Risedronate[284,299-301]	A	A	A	B
Teriparatide[284,302]	ND	A	A	ND
Testosterone (in males)[281]	ND	A	ND	ND
Zoledronic acid[303]	A	A	ND	ND

Primary prevention: Given within 3-4 months of initiation of glucocorticoid therapy; Secondary prevention: Treatment following an osteoporotic fracture or use of glucocorticoid for longer than 3-4 months; ND: No benefit demonstrated /no data.

The medications shown in Table 7-3 are effective at reducing bone loss in patients on GC compared to placebo (which typically consists of calcium and/or vitamin D supplements). There have been a few head-to head studies.

- In a 1-year study on primary and secondary prevention, one dose of intravenous (IV) zoledronic acid (ZA) significantly increased lumbar spine and femoral neck BMD compared to daily oral risedronate[303]
- In a 3-year study on secondary prevention, patients on recombinant human PTH 1-34 (r-PTH/teriparatide) had greater increases in lumbar spine, femoral neck and total hip BMD compared to those on alendronate[302]
- Two other studies have looked at denosumab compared to alendronate and risedronate
  - In a secondary prevention study, one year of denosumab 60 mg every six months, compared with alendronate 70 mg/week significantly increased lumbar spine, but not femoral neck or total hip BMD, after adjusting for baseline BMD values, age, sex, osteoporosis risk factors and the cumulative prednisolone doses received in one year[292]
  - In a 2-year study of both primary and secondary prevention, denosumab 60 mg every six months led to significantly greater gain in lumbar spine and total hip BMD compared to risedronate 5 mg daily[293]

In patients who have had a sub-optimal response to bisphosphonates, switching over to denosumab for one year led to a significant greater gain in lumbar spine BMD compared to continuing with the bisphosphonate, after adjusting for confounding factors. There was no difference in hip BMD.[304]

A reduction in vertebral fracture rates with have been shown with alendronate,[283] denosumab,[284] risedronate[301] and r-PTH/teriparatide[293] treatment. A meta-regression analysis suggested that alendronate is most efficacious in reducing vertebral fracture in patients on higher daily doses of GC, >7.5 mg daily compared to those on lower doses of GC.[305] In addition, a matched cohort-analysis also showed a reduction in hip fractures with alendronate and risedronate treatment.[299]

The treatment pathways are shown in Algorithm B.

- Treatment options depend on fracture risk (low/moderate/high), age (below or above 40 years) and childbearing potential
- Patients with a low fracture risk can be monitored with yearly clinical fracture risk assessment and BMD testing every 1-2 years depending on risk factors
- For patients with moderate to high risk, oral bisphosphonates are the first option
- Women of childbearing potential need to be counselled on not planning a pregnancy during treatment of GIOP as none of the drugs are recommended during pregnancy.
- Treatment should be continued as long as patients are on GC[273] **[Grade D, Level 4, ☑]**

After discontinuation of GC therapy, fracture risk decreases gradually towards baseline,[306] with most of the excess fracture risk disappearing within one year of stopping.[266] **[Level 2++]** Fracture risk should be re-assessed when GC is stopped; for those who remain at moderate to high risk, treatment should be continued until fracture risk is assessed to be low.[274] **[Grade D, Level 4]**

7.2 Renal osteodystrophy

Chronic kidney disease (CKD) affects 15.48% adults in Malaysia in 2018.[307] Mineral and bone disorder (MBD) is a common complication of CKD particularly in those on dialysis. Patients with CKD stages 1-2 and stages 3a-3b with normal parathyroid hormone levels, with osteoporosis and/or high risk of fracture should be managed as the general population.[308,309] **[Grade B, Level 1++]** For patients with more advanced CKD, the mainstay of treatment is to address the metabolic abnormalities associated with renal impairment, namely correction of acidosis, hyperphosphatemia and hypocalcaemia. **[Grade D, Level 2++]** Please refer to the 2017 KDIGO-CKD guidelines on MBD for further details on the management of CKD-MBD.[310]

7.3 Amenorrhoea

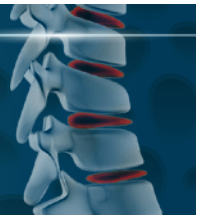
Extreme physical activity (leading to amenorrhoea in women), anorexia nervosa and hypogonadal disorders in young women may be associated with low BMD. Bone loss in amenorrhoeic women show the same pattern as in postmenopausal women. Treatment is with hormone replacement.[311] **[Grade A, Level 1+]** For patients with anorexia nervosa, weight loss should be reversed[312] and transdermal estrogen has been shown to increase BMD in mature adolescents.[313] **[Grade A, Level 1+]**

7.4 Drugs that induce osteoporosis

Drugs that can cause alteration in bone metabolism include glucocorticoids, gonadotropin releasing hormone (GnRH) agonist, aromatase inhibitor, anti-convulsant, anti-retroviral drugs, cyclosporin, tacrolimus, thiazolidinediones, exchange resins and long-term heparin. All patients should be encouraged to remain physically active and consume 800 IU vitamin D and 1000 mg calcium daily. If fracture risk is high, treatment with approved drugs should be considered. **[Grade B, Level 1++]**

SECTION 8:

OSTEOPOROSIS IN MEN



30% of hip fractures affect men[314] and they have a higher mortality from it than women.[315,316] 65% of osteoporosis in men is due to secondary causes[317] of which 20% is due to hypogonadism.[318]

8.1 Screening, clinical assessment and investigations for osteoporosis in men

The relationship between bone mineral density measurement (BMD) and fracture risk is considered to be similar in men and women. Osteoporosis screening tools for men may be useful to identify those that would likely have osteoporosis by BMD measurements.[336-338] Screening BMD is recommended by the Endocrine Society, International Society for Clinical Densitometry (ISCD) and National Osteoporosis Foundation (NOF) for all men ≥70 years old, or earlier if there are concomitant risk factors.[105,319,320] **[Grade C, Level 4]** Fracture risk can be calculated using the Fracture Risk Assessment Risk (FRAX®) calculator. Smoking and alcohol use disorder, which are risk factors for osteoporosis are more prevalent among men than women.[320]

Clinical, laboratory, and radiological assessments for osteoporosis in men are generally similar to women, but include assessment for male hypogonadism and/or androgen deprivation therapy for prostate cancer (see Algorithm C for the management of male osteoporosis).

8.2 Treatment of osteoporosis in men

Treatment of osteoporosis in men is similar to postmenopausal osteoporosis. Consider,

- Non-pharmacologic treatment: with emphasis on addressing smoking and alcohol use disorder when present[319] **[Grade C, Level 2++]**
- Calcium and Vitamin D supplementation: with supplementary calcium if dietary calcium is insufficient (see Table 5-3)[319] **[Grade C, Level 2++]**

- Pharmacological treatments which have shown to increase BMD and reduce fractures in men,
  - Bisphosphonates: alendronate, risedronate, zoledronic acid have been shown to increase bone density at lumbar spine and femoral neck in men, as well as reduce the risk of vertebral fracture in men[321-323] **[Grade A, Level 1++]**
  - Denosumab has been shown to increase bone density at the lumbar spine and femoral neck in men, but has no data on fracture risk reduction in men[324,325] **[Grade B, Level 1++]**
  - Teriparatide has been shown to increase bone density at the lumbar spine and femoral neck in men, but has no data on fracture risk reduction in men[326] **[Grade B, Level 1++]**

Follow up and surveillance for men with osteoporosis are similar with women (see Sections 3.6 and 5.13). **[Grade D, Level 4, ☑]**

SECTION 9:

FRACTURE LIAISON SERVICE

Sustaining a fragility fracture increases the risk of another fracture by at least two-fold.[327] However, this risk is not constant and is highest in the following 12 months after an index fracture.[327]

Despite the urgency to minimise future fracture risk, many individuals do not receive the necessary evaluation and appropriate secondary prevention.[328-330]

Fracture Liaison Service (FLS)[331] is a care-coordinator-based secondary fracture prevention programme. FLS systematically identifies, assesses, investigates, and appropriately treats patients with fragility fractures.

The role of the FLS

- Identification of individuals with fragility fractures within the healthcare institution (e.g. inpatient trauma wards, Emergency Department, or orthopaedic clinics)
- Evaluation of future fracture risk according to locally agreed protocols and guidelines
- Timely assessment of bone fragility (bone mineral density [BMD] assessment and secondary causes of osteoporosis) and falls risk
- Initiation of treatment
- Treatment review and appropriate follow up plan
- Patient education on optimising bone health
- Data and record keeping for audit and assessment of quality standards

Adapted from Chan DDC, et al. Arch Osteoporosis 2018.[331]

FLS requires a multi-disciplinary approach,[332] An effective FLS requires coordination with other healthcare professionals and services including bone densitometry services, specialist fall clinics, access to primary care, orthopaedic units and clinicians with osteoporosis expertise.

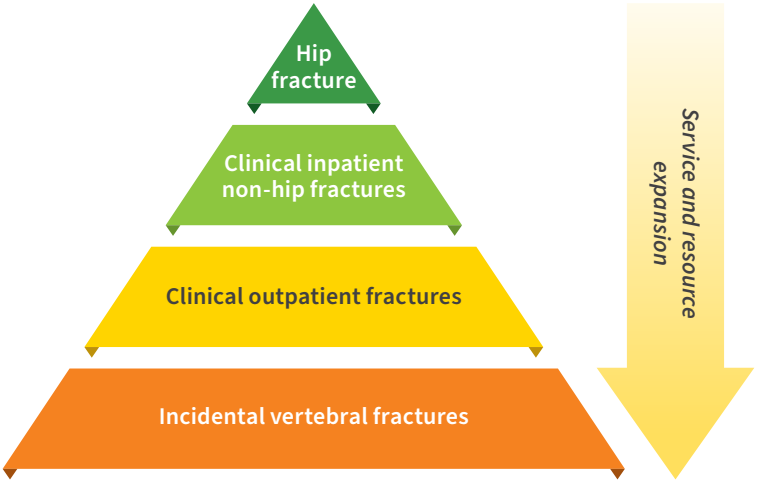
Initiating and sustaining FLS require[333] leadership, organisational support, stakeholder engagement and investment of resources (infrastructure, staff, and support systems).

Successful FLS has been shown to,[332]

- Increase the number of BMD testing performed
- Increase treatment initiation
- Improve treatment persistence
- Reduce re-fracture rates by half

FLS has been demonstrated to be cost-effective, supporting its place as an effective secondary prevention strategy.[333] A stepwise implementation has been suggested to allow systematic scaling up of FLS (Figure 9-A).[334]

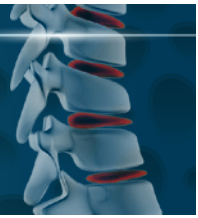
Figure 9-A. Scaling of services and resources when planning for an FLS



Adapted from Marsh D, et al. Osteoporos Int 2011.[334]

SECTION 10:

AUDIT QUESTION



To determine the number of low trauma/osteoporotic hip fractures that occur in the major public and private hospitals in Malaysia prospectively and, of that baseline number, to determine the number of patients put on osteoporosis treatment following their hip arthroplasty to prevent future fractures.

$$\text{Percentage of patients with low trauma/osteoporotic hip fracture and who have undergone hip arthroplasty on osteoporosis treatment} = \frac{\text{Number of patients with low trauma/osteoporotic hip fracture on osteoporosis treatment post-hip arthroplasty}}{\text{Total number of patients with low trauma/osteoporotic hip fracture who are post-hip arthroplasty}} \times 100\%$$

The audit parameter remains the same as the last version of the CPG as its uptake was poor.

SECTION 11:
IMPLEMENTING THE GUIDELINES

Implementation of the Clinical Practice Guidelines (CPG) is important as it helps in providing quality healthcare services based on best available evidence applied to the local scenario and expertise. Various factors and resource implications should be considered for the success of the uptake in the CPG recommendations.

11.1 Facilitating and limiting factors

The existing facilitating factors in implementing the recommendations in the CPG are:

- Availability of CPG to healthcare providers (hardcopies and softcopies)
- Regular conferences and updates on management of osteoporosis led by the Malaysian Osteoporosis Society and involving other professional societies or bodies (Malaysian Endocrine and Metabolic Society, Menopause Society of Malaysia, Academy of Family Physicians Malaysia, Malaysian Orthopaedic Association, Malaysian Society of Geriatric Medicine, Malaysian Society of Rheumatology)
- Public awareness campaigns on osteoporosis on World Osteoporosis Day and at other relevant times of the year

The existing limiting factors in implementing the recommendations in the CPG are:

- Different levels of care and wide variation in practice due to expertise, facilities and financial constraints
- Lack of awareness among healthcare providers on the importance of treatment of osteoporosis in high-risk patients
- Lack of awareness among the general public on the importance of bone health as they age

11.2 Potential resource implications

To implement the CPG, there must be dedicated efforts to:

- Ensure widespread distribution of CPG to healthcare providers
- Provide regular training to healthcare providers via effective seminars and workshops
- Involve multidisciplinary team at all levels of health care
- Encourage the formation of Fracture Liaison Services in all major hospitals that treat osteoporotic fractures

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DISCLOSURE STATEMENT

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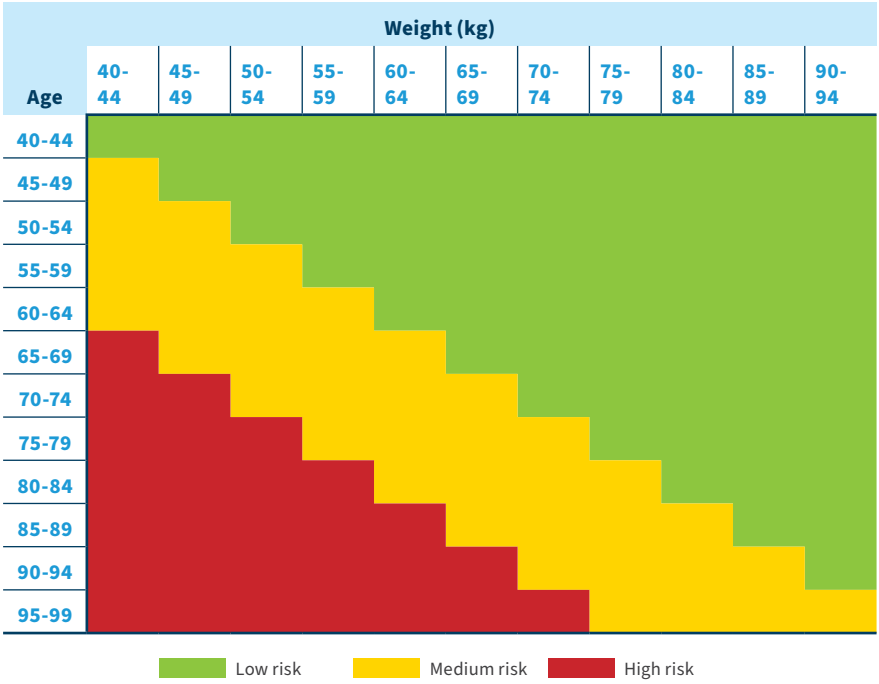
APPENDICES

Appendix 1. The Osteoporosis Self-Assessment Tool for Asians (OSTA)



Sourced from Yeap SS, et al. Int J Rheum Dis. 2013.[31]

Appendix 2. Bone mineral density measurement at various skeletal sites

Region of interest	Measurement
Spine	• Use PA L1-L4 for spine BMD measurement • Use all evaluable vertebrae and only exclude those that are affected by local structural change or artifact – use 3 vertebrae if 4 cannot be used; use 2 if 3 cannot be used • The T-score is only derived from the BMD of the evaluable vertebrae – do not use the BMD of excluded vertebrae • BMD-based diagnostic classification should not be made using a single vertebra. If only one evaluable vertebra remains after exclusion of others, base the diagnosis on a different valid skeletal site • Anatomically abnormal vertebrae may be excluded from analysis if it is clearly abnormal and non-assessable within the resolution of the system and there is >1.0 T-score difference between the vertebra in question and the one adjacent to it • The lateral spine should not be used for diagnosis but may have a role in monitoring
Hip	• Use the femoral neck or total proximal femur, whichever is the lowest • BMD can be measured at either hip. However, there are insufficient data to determine if mean T-scores from both hip BMDs can be utilised for diagnosis • The mean hip BMD can be used for monitoring, with total hip preferred
Forearm	• Use 1/3rd radius of the non-dominant forearm for diagnosis as the dominant forearm is not recommended

BMD, bone mineral density; PA: posterior-anterior.

Appendix 3. Calcium content of common foods

Calcium content of some common foods[335]

Food	Calcium content (mg)
Milk – high calcium (1 glass/200 ml)	500
Milk – skimmed (1 glass/200 ml)	250
Milk – full cream (1 glass/200 ml)	220
Yoghurt (1 cup/150 g)	200
Tofu (1 piece/150 g)	200
Dhal – yellow (1/2 cup/100 g)	170
Spinach (1 cup/56 g)	160
Ice-cream (1 cup/156 g)	150
Watercress/Sai-yong choy (1 cup/50 g)	100
Cheese – cheddar (1 piece/20 g)	100
Mussels (1 cup/160 g)	100
Ikan billis – dried without head and entrails (1/2 cup/20 g)	100
Sardine – canned (1 piece/40 g)	100
Baked beans (1 cup/240 g)	100
Sawi, cekur manis, kai lan or pucuk ubi kayu (1 cup/50-80 g)	100
Tempeh (1 piece/70 g)	50
Milk -soyabean (1 cup/200 ml)	40
Broccoli (1 cup/95 g)	40
Almonds (10 nuts/15 g)	30

Appendix 4. Falls evaluation parameters

Evaluation of falls should include the following parameters

Parameters	Focus
Focused history on fall incidents	• Frequency of falls • Activity during the fall • Presence of any prodromal symptoms before the fall • Where and when the falls occurred • History of unexplained falls or transient loss of consciousness should prompt further assessment of cardiovascular disorders such as carotid sinus hypersensitivity, vasovagal syndrome and arrhythmias, and neurological disorders
Medication review	• Focus specifically on falls risk increasing drugs, such as cardiovascular agents, psychotropic medications, analgesia, and antidiabetic medications
Assessment and identification of acute or chronic medical illnesses	• Especially age-related degenerative conditions such as Parkinson's disease, chronic musculoskeletal pain, knee osteoarthritis, urinary incontinence, stroke, and diabetes mellitus
Assessment of sensory impairment and functional assessment	• Include visual acuity and hearing impairment screening • For the older adults assess their activities of daily living, use of assistive devices and perceived fear of falling within their environment
Examination	• Examine the gait and balance with Timed up and Go Test (TUG Test) • Neurological status and cognitive screening • Cardiovascular assessment – heart rate, rhythm, postural blood pressure and baseline electrocardiogram

Appendix 5. Staging and descriptions of osteonecrosis of the jaw

Stage	Description
0 – Non-exposed bone variant	Patients with no clinical evidence of necrotic bone, but who present with non-specific symptoms or clinical and radiographic findings, such as: ***Symptoms:*** • Odontalgia not explained by an odontogenic cause • Dull, aching bone pain in the jaw, which may radiate to the temporomandibular joint region • Sinus pain, which may be associated with inflammation and thickening of the maxillary sinus wall • Altered neurosensory function ***Clinical findings*** • Loosening of teeth not explained by chronic periodontal disease • Periapical/periodontal fistula that is not associated with pulpal necrosis due to caries, trauma or restorations ***Radiographic findings*** • Alveolar bone loss or resorption not attributable to chronic periodontal disease • Changes to trabecular pattern–dense bone and no new bone in extraction sockets • Regions of osteosclerosis involving the alveolar bone and/or the surrounding basilar bone • Thickening/obscuring of periodontal ligament (thickening of the lamina dura, sclerosis and decreased size of the periodontal ligament space)
1	Exposed and necrotic bone or fistula that probes to bone, in patients who are asymptomatic and have no evidence of infection. These patients may also present with radiographic findings mentioned for stage 0 which are localised to the alveolar bone region.

Stage	Description
2	Exposed and necrotic bone, or fistula that probes to bone, with evidence of infection. These patients are typically symptomatic. These patients may also present with radiographic findings mentioned for stage 0 which are localized to the alveolar bone region.
3	Exposed and necrotic bone, or fistulae that probe to bone, with evidence of infection, and one or more of the following: • Exposed necrotic bone extending beyond the region of alveolar bone, i.e. inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla • Pathologic fracture • Extra-oral fistula • Oral antral/oral nasal communication • Osteolysis extending to the inferior border of the mandible or sinus floor

Adapted from Ruggiero SL, et al. J Oral Maxillofac Surg 2014.[183]

Appendix 6. Stages of chronic kidney disease

Stage 1: Normal or high GFR (GFR > 90 mL/min)
Stage 2: Mild CKD (GFR = 60-89 mL/min)
Stage 3A: Moderate CKD (GFR = 45-59 mL/min)
Stage 3B: Moderate CKD (GFR = 30-44 mL/min)
Stage 4: Severe CKD (GFR = 15-29 mL/min)
Stage 5: End Stage Kidney Disease (GFR <15 mL/min)

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