

Clinical Guidance
on Management
of
Osteoporosis
2012



Malaysian Osteoporosis Society



Academy of Medicine



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Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Federal Government Administrative Centre
62590, Putrajaya, Malaysia

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This Clinical Guidance is available on the following websites:

<http://www.osteoporosis.my>
<http://www.moh.gov.my>
<http://www.acadmed.org.my>
<http://www.msr.my>

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Clinical Guidance on Management of Osteoporosis

Committee Working Group

Chairperson

Chan Siew Pheng

Consultant Endocrinologist
Subang Jaya Medical Centre,
Subang Jaya, Selangor

Co-chairperson

Yeap Swan Sim

Consultant Rheumatologist
Subang Jaya Medical Centre,
Subang Jaya, Selangor

Expert Panel

Emily Goh Man Lee

Consultant Rheumatologist
Geneagles Intan Medical Centre, Kuala Lumpur

Winnie Chee

Dietician
International Medical University, Kuala Lumpur

Hew Fen Lee

Consultant Endocrinologist
Subang Jaya Medical Centre, Subang Jaya, Selangor

Lee Joon Kiong

Consultant Orthopaedic Surgeon
Assunta Hospital, Selangor

Lim Heng Hing

Consultant Orthopaedic Surgeon
Geneagles Intan Medical Centre, Kuala Lumpur

Premitha Damodaran

Consultant Obstetrician & Gynaecologist
Pantai Hospital Bangsar, Kuala Lumpur

Malik Mumtaz

Consultant Endocrinologist /
Consultant Nuclear Medicine Physician
Island Hospital, Penang

Reviewers

Tong Seng Fah

Primary Care Physician
Universiti Kebangsaan Malaysia, Kuala Lumpur

Gun Suk Chyn

Consultant Rheumatologist
Hospital Tuanku Ja'afar, Seremban

K. Parameshwaran

Consultant Orthopaedic Surgeon
Geneagles Medical Centre, Penang

Zanariah binti Hussein

Consultant Endocrinologist
Hospital Putrajaya, Putrajaya

Leonard KH Koh

Consultant Endocrinologist
Geneagles Medical Centre, Singapore

Zainal bin Fitri

Family Medicine Specialist
Klinik Kesihatan Putrajaya, Putrajaya

Levels of evidence and grades of recommendation

Level of evidence

Levels	Type of evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials (RCTs)
Ib	Evidence obtained from at least one RCT
IIa	Evidence obtained from at least one well designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies e.g. comparative studies, correlation studies, case-control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities, or both

Used by the National Guidelines Clearinghouse (www.guidelines.gov), Agency for Healthcare Research and Quality, U.S. Department of Health & Human Services, USA.¹

Grades of recommendation

Grade	Recommendation
A (evidence levels Ia and Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (evidence levels IIa, IIb and III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation
C (evidence level IV)	Required evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality

Modified from the Scottish Intercollegiate Guidelines Network (SIGN).²

STATEMENT OF INTENT

This Clinical Guidance is not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are a guide to clinical practice, based on the best available evidence at the time of development. Adherence to this guide may not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient in the light of clinical data presented by the patient and the diagnostic and treatment options available.

PREFACE

Osteoporosis is an important threat to the health and well-being of our population, in particular the elderly. The burden of osteoporosis and its related morbidity and mortality is expected to rise as our population ages. The awareness of osteoporosis and more importantly its related fracture risk among the medical and general public has increased and I am glad to say that the Malaysian Osteoporosis Society continues to play a spearheading role in this.

Knowledge does not stagnate and therefore practice needs to keep pace. It has therefore become necessary to update the Clinical Practice Guidelines (CPG) on Management of Osteoporosis. There has been a greater usage and accessibility of DXA scanners to measure bone mineral density and thus proper interpretation becomes an important issue. This allows the early detection of low bone mass but it remains important to put the place of DXA scanning in perspective. The new recommendation is to assess and treat fracture risk and not mere numbers so the overall assessment of risk is essential. There are new anti-resorptive agents available and there is the exciting prospect of reliably increasing bone by stimulating bone formation. With improved assays and measurement of bone turnover markers that are more readily available and accurate, their place in monitoring needs to be addressed.

Once again a multi-disciplinary panel of experts have come together to plough through a burgeoning literature on osteoporosis and related topics to produce this update. The panel reviewed the current and most recent literature since the last CPG published in 2006 to update the document, which we have called a “Clinical Guidance”. It is important to accept that we cannot be comprehensive in all aspects. Subtle aspects of related topics such as menopause are addressed elsewhere. We must congratulate the panel for their tireless effort in the realisation of the CPG update.

We hope the Clinical Guidance will be of use to all practicing medical practitioners.



Chan Siew Pheng

Chairperson

Clinical Guidance Working Group



Yeap Swan Sim

Co-Chairperson

Clinical Guidance Working Group

KEY STATEMENTS AND RECOMMENDATIONS

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 architecture, turnover, damage accumulation, and mineralisation.

(Level IV)

Classification is based on bone mineral density (BMD). Osteoporosis is defined by BMD of more than -2.5 SD from the young adult mean (T-score) and osteopenia when the T-score is between -1.0 and -2.5 .

Observational studies suggest that a similar cut-off point to that used in women can be taken for diagnosis in men.

(Level IV)

The Clinical significance of osteoporosis lies in the resulting fracture. The exact magnitude in Malaysia is not known but hip fracture incidence in 1996-1997 in the over 50 years of age is 90/100,000 and is likely to increase with our ageing population.

(Level III)

The risk of fracture increases progressively with decreasing BMD. Risk of fractures increases approximately two fold for each SD decrease in BMD.

(Level Ia)

In those with a low trauma fracture, a BMD measurement, though advisable, is not necessary before starting therapy.

(Grade C, Level IV)

In addition to the diagnosis of osteoporosis, there should be fracture risk assessment and exclusion of secondary causes of osteoporosis.

(Grade C, Level IV)

BMD measurement is recommended especially when assessment would influence management (Table 7) and may save more resources than undirected use of treatment in all patients.

(Grade C, Level IV)

The gold standard for measuring BMD is dual-energy x-ray absorptiometry (DXA). DXA still remains the recommended method in the diagnosis of osteoporosis and monitoring the effect of therapy. Other methods for measuring BMD such as quantitative computed tomography (QCT) and quantitative ultrasound (QUS) are not recommended for diagnosing osteoporosis but QUS may help in case-finding.

(Grade C, Level IV)

FRAX is a fracture risk assessment tool used to evaluate the 10-year probability of hip and major osteoporotic fracture risk that integrates clinical risk factors and bone mineral density at the femoral neck in its calculations. Until more Malaysian data are available, it is recommended to use the Singapore prediction algorithm.

(Grade B, Level III)

OSTA can be used to screen postmenopausal women for further assessment of osteoporosis.

(Grade B, Level III)

Population-based strategies for the prevention of osteoporosis include life-style modification such as adequate calcium and vitamin D intake, exercise, reducing smoking and alcohol intake, for those at risk.

(Grade C, Level IV)

Table 1. The strength of recommendations concerning prevention of osteoporosis is summarised in the following table:

Intervention	BMD Improvement	Decrease Vertebral Fracture Rate	Decrease Hip Fracture Rate
Exercise	A	-	-
Calcium and Vitamin D supplements	A	A	A
Dietary calcium intake	B	-	-
Smoking cessation	C	-	-
Reduced alcohol consumption	C	-	-
Prevention of falls	-	-	B
Estrogen	A	A	A
Raloxifene	A	A	-
Alendronate	A	A	-
Tibolone	A	A	-

After assessment, treatment can be considered for postmenopausal women if they had a previous low trauma hip, vertebral or wrist fracture, or have a T-score ≤ -2.5 . In patients with osteopenia, initiation of treatment is recommended with a FRAX fracture probability of more than 3% at the hip or 20% for major osteoporotic fracture at 10 years.

(Grade C, Level IV)

Table 2. The strength of recommendations concerning interventions in the treatment of osteoporosis is shown in the following table:

Intervention	BMD Improvement	Decrease Vertebral Fracture Rate	Decrease Hip Fracture Rate
Alendronate	A	A	A
Risedronate	A	A	A
Zoledronate	A	A	A
Ibandronate	A	A	-
Strontium	A	A	A
Denosumab	A	A	A
Estrogen	A	A	A
Raloxifene	A	A	-
Calcitriol / Alfacalcidol	A	A	C
Calcium (± vitamin D)	A	A	B
r-PTH	A	A	-

The recommended daily intake for calcium is 1000mg (both dietary and supplements) and for vitamin D is 800IU.

(Grade C, Level IV)

The choice of drug for established osteoporosis, especially those with previous fracture, must be an agent shown not only to increase BMD, but also shown to reduce fracture both at the spine and hip.

(Grade A, Level Ia)

Hip fractures should be surgically managed promptly to allow early ambulation. Spine and wrist fractures may need operative intervention.

(Grade C, Level IV)

Patients on prednisolone more than 5mg daily or its equivalent, for more than 3 months, should be assessed for the presence of glucocorticoid-induced osteoporosis and treated as required.

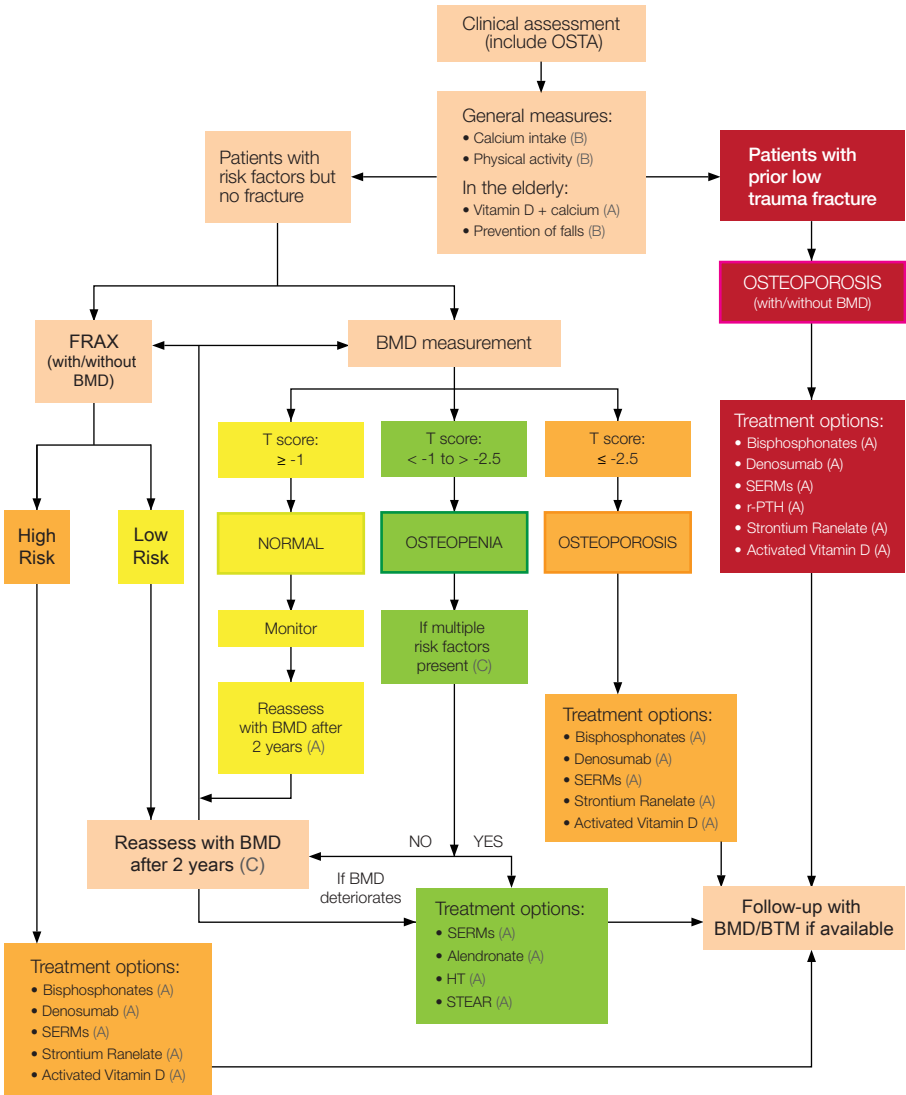
(Grade C, Level IV)

Secondary causes of osteoporosis should be excluded in men. Bisphosphonates, and PTH, denosumab and strontium have been shown to be effective, and androgen is useful in hypogonadal men.

(Grade A, Level Ib)

Figure 1

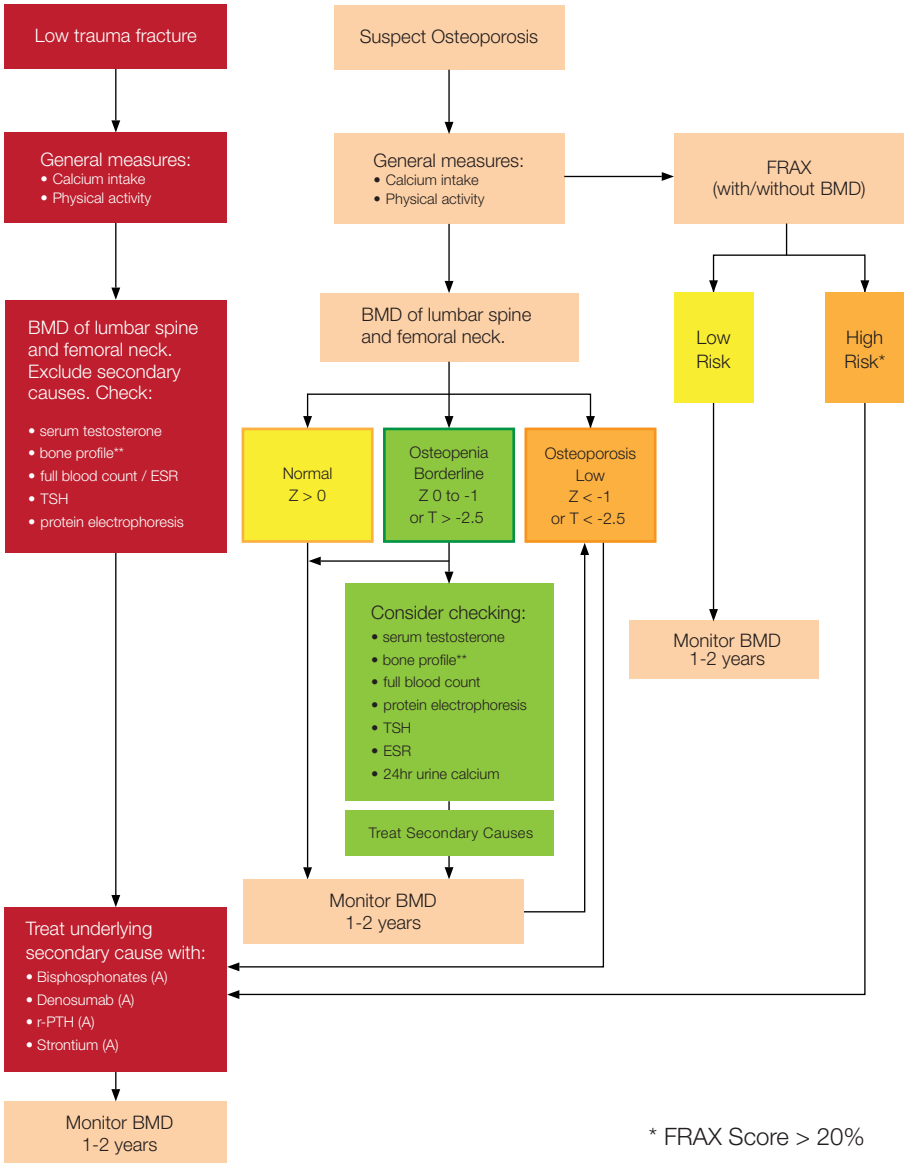
Algorithm for the management of postmenopausal osteoporosis



The treatment options found in the algorithm for the management of postmenopausal osteoporosis reflects the order of preference according to current medical evidence. The level of evidence is not a yardstick for comparing relative efficacy. There are few comparative studies between therapeutic agents but the therapeutic aim is for clinical fracture reduction rather than an increase in BMD. Therefore, agents with clinical fracture reduction are ranked higher in the hierarchy of therapeutic choice than agents with only BMD data.

Figure 2

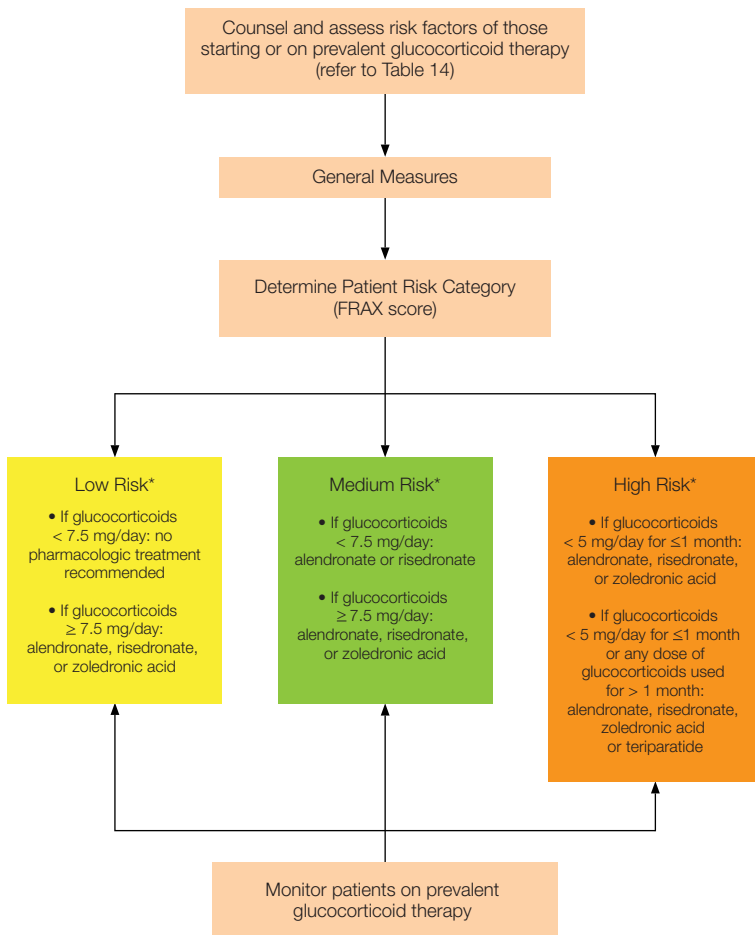
Algorithm for the management of male osteoporosis



* FRAX Score > 20%

** Bone Profile = Calcium, phosphate, alkaline phosphatase, albumin, creatinine
 ESR = Erythrocyte Sedimentation Rate
 TSH = Thyroid-stimulating hormone

Approach to postmenopausal women and men age > 50 years initiating or receiving glucocorticoid therapy³



* for low and medium-risk patients, recommendations are for an anticipated or prevalent duration of > 3 months of glucocorticoid treatment

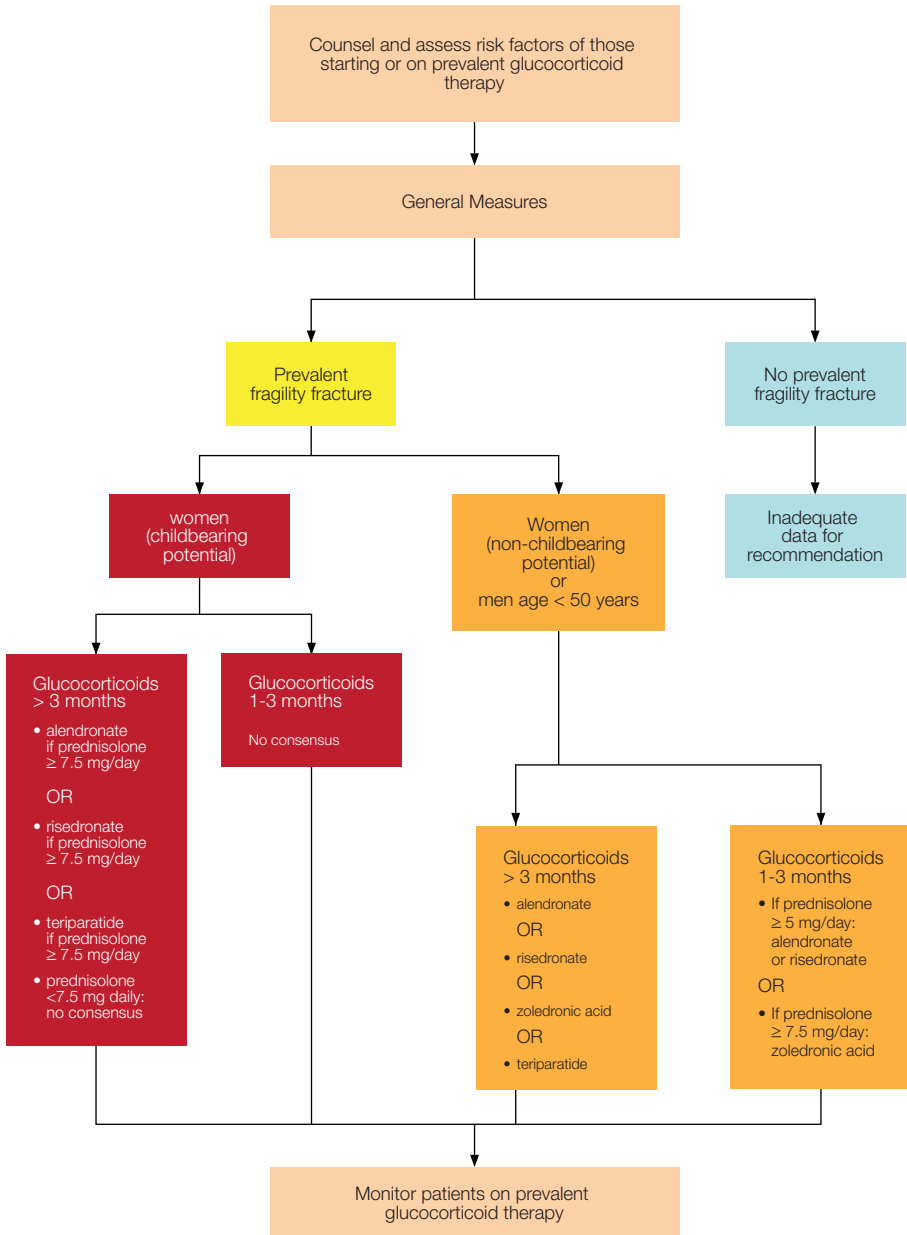
* **FRAX score**

Low Risk (< 10%)

Medium Risk (10%-20%)

High Risk (> 20%)

Approach to premenopausal women and men age < 50 years initiating or receiving glucocorticoid therapy³



1. BACKGROUND

1.1 Guidance Development

In 2001, the Malaysian Osteoporosis Society, in collaboration with Ministry of Health and Academy of Medicine produced the first clinical practice guidelines for the management of osteoporosis. This was updated in 2006. Since then, the field of osteoporosis has continued to advance and it is timely for a review and update.

1.1.1 Methodology

The previous Clinical Practice Guidelines published in 2006 was used as the baseline. To update the document, a systematic review and literature search by the members of the Working Group, using PubMed (MEDLINE) and The Cochrane Library, identified all relevant articles on osteoporosis and its assessment, diagnosis and treatment, from 2005 to 2011. The date 2005 rather than 2006 was chosen so that all studies published just before and after the last guidelines would be reviewed and none inadvertently overlooked. The studies were assessed and graded with the levels of evidence as used by the National Guideline Clearinghouse, Agency for Healthcare Research and Quality, U.S. Department of Health & Human Services, USA (Page 4). For each statement, studies with the highest levels of evidence were used to frame the statements. The grade of recommendation was taken from the Scottish Intercollegiate Guidelines Network grading system (Page 5).

This guidance will be updated in 5 years' time.

1.2 Objectives

This guidance is not to be viewed as a protocol, but provide a framework to:

- Assist doctors in the diagnosis and management of osteoporosis without restricting the physician's individual judgment
- Provide a review of the therapeutic agents available for the treatment of osteoporosis, with the aim of reducing fracture, and its accompanying morbidity and mortality
- Aid primary care physicians in deciding when to refer patients with difficult problems to the relevant specialists

1.3 Clinical Questions

The clinical questions addressed in this guidance are:

- How do we identify patients at risk of osteoporosis?
- What are the current best practices in the management of postmenopausal women with osteoporosis, male osteoporosis & glucocorticoid-induced osteoporosis?
- What are the risks and benefits of osteoporosis treatments?

1.4 Target Population

This guidance is to be applied to adults above the age of 18 years, in particular, in postmenopausal women with osteoporosis, men with osteoporosis and patients with glucocorticoid-induced osteoporosis.

1.5 Target Group

This guidance would be useful for all health care professionals who manage patients with osteoporosis, such as primary care physicians/general practitioners, gynaecologists, orthopaedic surgeons, rheumatologists and endocrinologists as well as paramedical personnel such as nurse practitioners, nurse specialists, dieticians and physiotherapists.

2. 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.⁴

The WHO working group⁵ defines osteoporosis in women on the basis of the criteria shown in Table 3. Bone mineral density (BMD) peaks during the third decade of life and declines with advancing age. In women, this decline accelerates with menopause for 5 -10 years (Figure 5).

(Level IV)

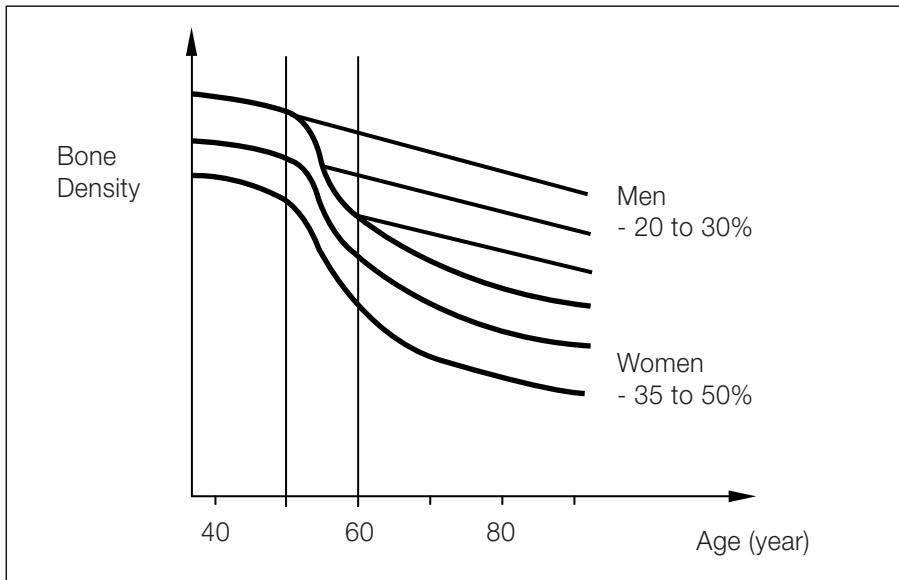
Table 3: The World Health Organisation (WHO) Working group classification of osteoporosis for postmenopausal women²

Normal	Bone mineral density (BMD) ≥ -1.0 SD of young adult reference range (T-score ≥ -1.0)
Osteopenia	BMD between -1.0 SD and -2.5 SD below the young adult mean ($-1.0 > \text{T-score} > -2.5$)
Osteoporosis	BMD ≤ -2.5 SD of the young adult mean (T-score ≤ -2.5)
Severe / Established Osteoporosis	BMD ≤ -2.5 SD of the young adult mean with the presence of 1 or more fragility fractures

* T score: comparison with young adult mean

In men older than 50, osteoporosis may be diagnosed if the T-score of the lumbar spine, total hip or femoral neck is -2.5 or less.⁶

Figure 5: Bone Loss During Adult Life⁷



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.^{8,9}

(Level III)

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 4).⁷

Table 4: Incidence of Hip Fracture in Malaysia by Age Group 1997¹⁰

Age Group	Incidence by Age Group (per 100,000)		
	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

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.¹⁰

The direct hospitalisation cost for hip fractures in 1997 is estimated at RM 22 million. This is a gross underestimate of the total economic burden, as it does not take into account the costs incurred in rehabilitation and long term nursing care. Therefore, in an ageing population this cost will escalate without appropriate intervention.¹⁰

(Level III)

3. CLASSIFICATION AND RISK FACTORS

3.1 Primary Osteoporosis

- Postmenopausal osteoporosis. Accelerated bone loss related to oestrogen deficiency
- Age-related osteoporosis. This occurs in both men and women
- Idiopathic (rare)

3.2 Secondary Osteoporosis (See Table 5)

Table 5: Secondary Osteoporosis

1. Endocrine
 - Cushing's syndrome
 - Hypogonadism
 - Thyrotoxicosis
 - Hyperparathyroidism
2. Drugs
 - Glucocorticoids
 - Heparin
 - Anticonvulsants (phenytoin)
 - Immunosuppressants
 - Thiazolidinediones
 - Oncology (e.g. Aromatase inhibitors, androgen deprivation therapy)
3. Chronic Diseases
 - Renal impairment
 - Liver cirrhosis
 - Malabsorption
 - Chronic inflammatory polyarthropathies (e.g. rheumatoid arthritis)
4. Others
 - Nutritional deficiency e.g. anorexia nervosa
 - Multiple myeloma and malignancy
 - Osteogenesis imperfecta
 - Post-gastrectomy / gastric bypass surgical procedures

3.3 Risk factors for Osteoporosis:

Osteoporosis is a silent disease without any symptoms in most patients until fractures have occurred. While population screening is not cost effective, identification of risk factors will help in case finding.¹¹

(Grade C, Level IV)

The major factors associated with an increased risk of osteoporotic fracture in postmenopausal women are shown in Table 6.¹²

Table 6: Risk Factors¹²

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

4. DIAGNOSIS

4.1 Clinical Presentation

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

1. Increasing dorsal kyphosis (Dowager's hump)
2. Low trauma fracture
3. Loss of height
4. Back pain

4.2 Diagnosis

The diagnosis of primary osteoporosis is made after excluding secondary causes of bone loss. A clinical evaluation, which includes a careful history, physical examination and appropriate laboratory investigations, is mandatory.

As multiple risk factor assessment does not predict bone mass with sufficient precision,¹³ **(Grade B, Level IIa)** bone mineral density (BMD) remains the mainstay in decision making to identify the 'at-risk' patient requiring further investigation.

(Grade C, Level IV)

When a patient presents with a low trauma fracture, osteoporosis is a presumptive diagnosis. BMD measurement with dual energy x-ray absorptiometry (DXA) is advised. However, in the absence of this facility, treatment should still be initiated. In the absence of a fragility fracture, the **gold standard** for the diagnosis of osteoporosis remains the measurement of BMD using DXA.

(Grade C, Level IV)

If a BMD measurement is not available, calculating the risk of fractures using Fracture Risk Assessment Tool (FRAX) can help in deciding treatment strategies.

(Grade B, Level III)

Fracture Risk Assessment Tool (www.shef.ac.uk/frax)

Fracture Risk Assessment Tool (FRAX) estimates the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm), for untreated patients between age 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.^{14,15}

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, 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/total hip BMD is to be used. BMD input from non-hip sites has not been validated with FRAX and is therefore not recommended.¹⁴

The treatment interventions in FRAX have been partly based on cost-effectiveness, for which there is no Malaysian data. Notwithstanding that, we would propose using the National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis (2010),¹⁶ in that postmenopausal women and men over the age of 50 should be considered for treatment if they had a previous hip or vertebral fracture or a T-score ≤ -2.5 on DXA after exclusion of secondary causes of osteoporosis. In patients with osteopenia, initiation of treatment is recommended with a fracture probability of more than 3% at 10 years for hip or 20% at 10 years for major osteoporosis related fracture.

If FRAX is not accessible, elderly individuals over 65 years of age with multiple risk factors who are at sufficiently high risk for osteoporosis, can be started on treatment.^{17,18}

(Grade C, Level IV)

Recommendation

The Singapore prediction algorithm should be used when using the FRAX tool. Treatment can be started in patients with osteopenia when the 10-year fracture probability is more than 3% for hip and more than 20% for major osteoporosis-related fractures.

(Grade C, Level IV)

4.3 Screening

Population-based screening is not recommended given the constraints of current methods of measurement and lack of evidence for cost effectiveness. However, a BMD measurement is recommended for all women above 65 and men above 70 years old.⁶

(Grade C, Level IV)

A simple clinical screening tool, based on age and weight, Osteoporosis Self-Assessment Tool for Asians (OSTA), was developed for postmenopausal Asian women. Women in the high risk category and those in the moderate risk category with additional risk factors (e.g. glucocorticoid use, hypogonadism, immobilisation) for osteoporosis should be recommended for DXA (See Appendix 1).

Recommendation

OSTA can be used to screen postmenopausal women for further assessment of osteoporosis.

(Grade B, Level III)

4.4 Investigations

The main aims of investigations are to:

1. Confirm the diagnosis of osteoporosis
2. Assess fracture risk
3. Exclude secondary causes

Initial investigations include:

1. Full blood count and erythrocyte sedimentation rate (ESR)
2. Bone profile: serum calcium, phosphate, albumin
3. Alkaline phosphatase
4. Renal function
5. Plain X-rays - lateral thoraco-lumbar spine or hip (as indicated)

Radiological osteopenia is apparent in plain X-rays only after more than 30% of bone loss has occurred.

Other investigations may be done as indicated based on clinical suspicion of secondary causes [e.g. free thyroxine T4 (FT4), thyroid-stimulating hormone (TSH), testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), urine Bence Jones protein, serum protein electrophoresis].

4.5 Specific Investigations

4.5.1 Densitometry

BMD measurement gives an accurate reflection of bone mass and helps in establishing the diagnosis of osteoporosis (Table 3). It is important to use race-specific reference ranges when available. BMD results are reported as T-scores (comparison with the young adult mean) and Z-scores (comparison with the mean of individuals of the same age) (Figure 6). The risk of fracture is increased two fold for each SD reduction of T-score in BMD.¹⁹

(Grade A, Level Ia)

Currently available methods in Malaysia for measuring BMD include:

- a) Dual energy X-ray absorptiometry (DXA)
- b) Quantitative computed tomography (QCT)

a) DXA

The gold standard for diagnosis is DXA, which is measured at the hip and lumbar spine. The procedural standard for performing DXA should be followed to ensure quality and consistency. Prediction of fracture risk is site-specific. When site-specific measurements are not available, other skeletal sites can be used to provide an adequate estimation of fracture risk.

Peripheral DXA (phalanges / distal radius / calcaneum) is useful for site-specific fracture risk prediction. Forearm BMD measurement can be used to predict fracture risk. However, their predictive capacity for hip fracture appears to be less than that of DXA of the spine and hip.

The decision to measure BMD should be based on an individual's risk profile and is indicated if the results will influence management. (See Table 7)

(Grade C, Level IV)

Recommendation

BMD measurement with DXA remains the gold standard for the diagnosis of osteoporosis. The decision to measure BMD should be based on an individual's risk profile and is indicated if the results will influence management.

(Grade C, Level IV)

Figure 6. Expression of Bone Mineral Density as measured by DXA

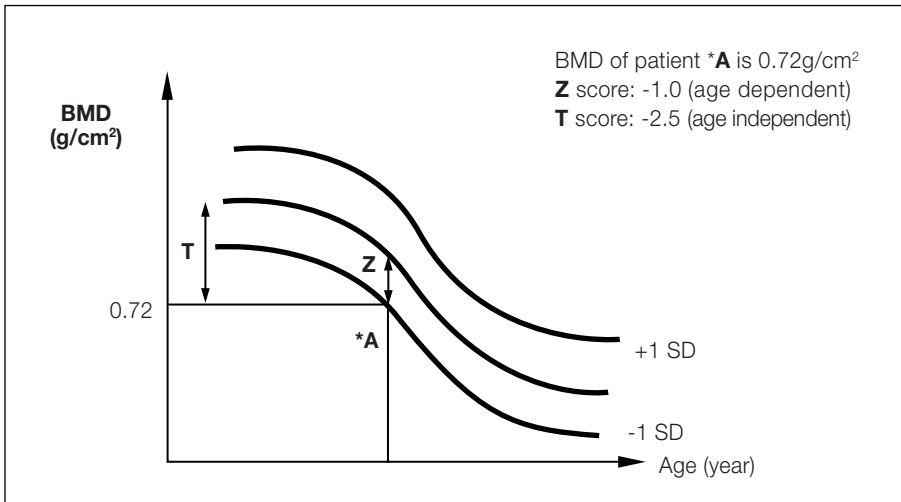


Table 7: Indications for BMD Measurement*

1. All women aged 65 and above and men aged 70 and above⁶

2. Presence of strong risk factors

Estrogen deficiency

- Premature menopause (< 45 years of age) including surgical menopause
- Prolonged secondary amenorrhoea
- Hypogonadism

Glucocorticoid therapy (see Section 8.1 on Glucocorticoid-Induced Osteoporosis)

Maternal family history of hip fracture

Low body mass index (<19 kg/m²)

Other conditions associated with osteoporosis

- Anorexia nervosa
- Malabsorption
- Hyperparathyroidism
- Hyperthyroidism
- Prolonged immobilisation
- Cushing's syndrome
- Post-bariatric surgical bypass
- Drugs [e.g. aromatase inhibitors, Gonadotropin-releasing hormone (GnRH) agonists]

3. Radiological osteopenia and/or vertebral deformity

4. Previous low trauma fractures of hip, spine and/or wrist

5. Loss of height, thoracic kyphosis

6. Low weight for age (OSTA) for postmenopausal women (Appendix 1)**

* BMD should only be measured in postmenopausal women who are willing to consider available interventions.

** OSTA = Osteoporosis Self-assessment Tool for Asians

b) QCT

Quantitative computed tomography (QCT) is an alternative technique for measuring bone density in the axial skeleton.²⁰ It is able to measure vertebral volumetric bone density. The main limitations are the lack of availability in Malaysia and a higher radiation dose compared to DXA.^{21,22}

4.5.2 Quantitative Ultrasound (QUS)

QUS in the diagnosis and monitoring of treatment is not recommended. Problems with this modality include the diversity of techniques, the lack of standardisation and comparable local normal ranges. QUS appears to be a good predictor of fracture and is currently recommended as a screening tool. The decision to treat should not be based on the results of QUS. The criteria for diagnosis and recommending treatment based on ultrasound are not well established.^{23,24,25}

(Grade C, Level IV)

Women with low QUS results should be referred for BMD measurement.

(Grade C, Level IV)

4.5.3 Bone Turnover Markers

Bone turnover markers (BTM) are useful to identify patients at high risk of future fractures.^{26,27,28} It can also be used to evaluate treatment efficacy and compliance to therapy.^{28,29,30} They should not be used for the diagnosis of osteoporosis. Changes in level of BTM can be seen within 3-6 months after initiation of drug therapy.^{26,27,28}

(Grade B, Level IIa)

Table 8: Currently available biochemical markers

Resorption	Formation
Serum C-telopeptide (CTX)	N-terminal propeptide of type 1 procollagen (P1NP)
Urinary deoxypyridinoline (DPD)	Bone specific alkaline phosphatase
Urinary N-telopeptide (NTX)	Osteocalcin

Serum CTX (bone resorption) and P1NP (bone formation) are used in the management of patients with osteoporosis.²⁹

(Grade B, Level IIa)

4.6 Monitoring of Therapy

The aim of monitoring is to assess the response to treatment.

- Patients should have regular clinical assessments
- Currently, monitoring of treatment using QUS and peripheral DXA is not recommended
- If biochemical markers are available, two separate baseline measurements of the same marker need to be carried out followed by one repeat measurement 2-3 months after initiating therapy and yearly thereafter, if indicated. These measurements should be taken at the same time of the day to minimise the effect of diurnal variation.

(Grade C, Level IV)

5. PREVENTION OF OSTEOPOROSIS AND FALLS

5.1 Nutrition

Nutrition is important during bone growth as well as aging. In addition to ensuring adequacy of calcium and vitamin D, a balanced diet throughout life is important for bone health.³⁰

(Grade B, Level IIa)

Maintenance of an adequate protein and energy intake is important especially in the elderly.³¹

(Grade B, Level III)

Adequate protein intake helps minimize bone loss among patients who have sustained hip fractures.^{32,33}

(Grade C, Level IV)

In one study, patients with hip fracture who received supplemental protein had shorter hospital stays and better functional recovery.³³

(Grade B, Level IIb)

5.1.1 Calcium

Individuals of all ages should have an adequate calcium intake to maintain bone health.

(Grade A, Level Ia)

The recommended levels of calcium intake for Malaysians of all age groups are shown in Table 9. Attempts should be made to achieve these levels for maximum benefit to bone health.

(Grade C, Level IV)

For women 50 years old or older, the recommended daily calcium intake is 1000 mg. This represents the total calcium intake (diet plus calcium supplements, if applicable).³⁴

Table 9: Suggested Daily Calcium Intake³⁴

	Age	Recommended Intake
Infants ^a	0 - 6 months	300 mg (breast-fed) 400 mg (non-breast-fed)
	6 - 12 months	400 mg
Children	1 - 3	500 mg
	4 - 6	600 mg
	7 - 9	700 mg
Adolescents (boys & girls) ^b	10 - 18	1000mg
Men	19 - 49	800 mg
	> 50 years	1000 mg
Women	19 - 49	800 mg
	> 50 years	1000 mg
Pregnant ^c Lactating	Third trimester	1000 mg 1000 mg

- a The absorption of calcium from human breast milk is higher than from baby formula, therefore the calcium requirement for non breast-fed babies is higher.
- b The calcium recommendation of Malaysian adolescents is 1000 mg/day based on a moderate animal protein intake of 20-40 g/day.³⁴
- c During pregnancy and lactation, calcium absorption is increased and fetal bone mineralisation can be obtained with no detectable mobilisation of maternal bone for this purpose. However, in Malaysia where habitual calcium intake is low, a high calcium intake may possibly benefit the fetus. The recommendation for calcium during pregnancy and lactation is 1000 mg/day.³⁵

When dietary intake is insufficient, calcium supplementation may be needed. The absorption of calcium supplements is highly variable ranging from 20-40% depending on the formulation as shown in Table 10.

For optimal absorption, the amount of calcium should not exceed 500 to 600 mg per dose, irrespective of the calcium preparation. For patients requiring more than 600 mg of calcium supplement daily, the dose should be divided.^{36,37,38}

(Grade B, Level IIa)

Table 10: Studies investigating calcium absorption from different sources³⁸

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)

Recent conflicting data suggest that excessive calcium supplementation is associated with cardiovascular events.^{39,40,41} A meta-analysis suggested that calcium supplements taken without vitamin D increase the risk of myocardial infarction, relative risk 1.27 (95% CI 1.01 -1.59).⁴⁰

(Level Ia)

A prospective randomised interventional trial on calcium carbonate showed no excess cardiovascular risk.⁴² Another prospective randomised trial with vitamin D 800 IU and calcium 1000 mg daily compared to placebo showed no difference between both groups in vascular mortality.⁴³ The results of these studies are not directly comparable, as different endpoints were used.

(Level Ib)

The risk of cardiovascular events is predominantly observed in studies with higher doses of calcium supplements (1000-2000 mg) and lower doses are deemed to be safe.

Calcium from dietary sources was not associated with a higher risk of coronary heart disease.⁴² Therefore, it is encouraged to have adequate calcium intake from food sources.⁴⁴ (The calcium content of some common foods is given in Appendix 2)

5.1.2 Vitamin D

It is important to ensure sufficiency of vitamin D among children and adults to prevent osteoporosis.⁴⁵

(Grade A, ;Level 1a)

Blood levels of 25(OH)D provide the best index of vitamin D stores. It has been suggested that levels of 25(OH)D of >20 ng/mL (50 nmol/L) is the minimum level required for skeletal health.⁴⁵ However, the Endocrine Society recommends a level of 25(OH)D of >30 ng/mL (>75 nmol/L) for optimal musculoskeletal health.¹⁸⁰

For adults 50 years old or older, the Malaysian Recommended Nutrient Intake advocates 400 IU of vitamin D per day, but many experts recommend at least 800 to 1000 IU per day. Elderly who are institutionalised, immobile, lack outdoor activities and have a poor diet will benefit from at least 800 IU vitamin D supplementation daily.⁴⁶

Vitamin D supplements are available as ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). With daily dosing, vitamin D2 and D3 appear to be equally potent⁴⁷ (**Level 1a**), but with intermittent (weekly or monthly) dosing, vitamin D3 appears to be about 3 times more potent than vitamin D2⁴⁸ (**Level IIa**)

Vitamin D supplementation has also been shown to improve muscle strength, balance, and risk of falling (**Grade B, Level IIa**) as well as improve survival.^{49,50} (**Grade A, Level Ia**)

In a recent analysis of calcium with or without vitamin D supplementation, incorporating data from the Women's Health Initiative study, the relative risk for myocardial infarction in women without baseline personal calcium supplementation, was 1.24 (1.07–1.45, p=0.004) and the composite of myocardial infarction or stroke 1.15 (1.03-1.27, p=0.009). (**Level Ia**)

This suggests that addition of vitamin D did not reduce the elevated risk observed with calcium supplementation.³⁹

Recommendation

The recommended daily intake for calcium is 1000 mg (both dietary and supplements) and for vitamin D is 800 IU.

(Grade C, Level IV)

5.1.3 Body Weight

Low body weight and excessive dieting is associated with low bone mineral status and increased fracture risk⁵¹

(Grade B, Level IIa)

Maintenance of a body mass index of not less than 19 kg/m² is recommended for prevention of osteoporosis.⁵

(Grade C, Level IV)

5.1.4 Caffeine intake

Patients should be advised to limit their caffeine intake to less than 1 to 2 servings (240 to 360 mls in each serving) of caffeinated drinks per day.

(Grade B, Level III)

Several observational studies have shown an association between consumption of caffeinated beverages and fractures.

(Level III)

Caffeine intake leads to a slight decrease in intestinal calcium absorption and an increase in urinary calcium excretion.^{52,53}

5.1.5. Smoking

Cigarette smoking increases osteoporotic fracture risk and thus should be avoided.⁵⁴

(Grade B, Level IIa)

5.1.6. Alcohol intake

Excessive intake of alcohol should be avoided because alcohol has detrimental effects on fracture risk.⁵⁵

(Grade B, Level IIa)

5.2 Exercise

Regular physical activity, in particular weight-bearing exercise (e.g. brisk walking, 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.⁵⁶

(Grade C, Level IV)

The individual's health status should be taken into consideration when recommending an exercise programme.

5.3 Prevention of falls

Most osteoporosis-related fractures, especially in the elderly, are a consequence of decreased BMD and falls.⁵⁰

Table 11: Factors increasing risk of falls

Poor balance
Reduced muscle strength
Low vitamin D levels
Poor vision
Diseases of nervous & musculoskeletal systems
Excessive alcohol consumption
Certain medications (e.g. sedatives, anti-hypertensives)
Hazards in the home (e.g. steps, inadequate lighting, slippery floors)

5.3.1 Evaluation of Falls

Physicians caring for older patients should integrate fall assessment into the history and physical examination.⁵⁷

(Grade C, Level IV)

Older persons who present for medical attention because of a fall, report recurrent falls in the past year, or demonstrate abnormalities of gait and/or balance should have a fall evaluation performed.⁵⁸

(Grade C, Level IV)

A fall evaluation is defined as an assessment that includes the following: history of fall circumstances, medications, acute or chronic medical problems, and mobility levels; an examination of vision, gait and balance, and lower extremity joint function; an examination of basic neurological function, including mental status, muscle strength, lower extremity peripheral nerves, proprioception, reflexes, tests of cortical, extrapyramidal, and cerebellar function; assessment of basic cardiovascular status including heart rhythm and postural blood pressure.⁵⁸

5.3.2 Recommendations for Prevention of Falls	
RECOMMENDATIONS^{59,60}	STRENGTH AND LEVEL OF EVIDENCE
Patients should receive a multifactorial risk assessment and intervention because it is the most consistently effective strategy to prevent falls	Grade A, Level Ia
Home hazard assessment and modification is recommended for patients with a history of falls	Grade A, Level Ia
Exercise and physical therapy are recommended to prevent falls and injuries from falls	Grade A, Level Ia
Evaluation of medications and withdrawal of medications that increase the risk of falling is recommended	Grade B, Level IIa

In long-term care and assisted living settings, multifactorial interventions should include: staff education programs; gait training and advice on the appropriate use of assistive devices; and review and modification of medications, especially psychotropic medications.⁵⁸

(Grade B, Level IIa)

5.3.3 Strategies for the Prevention of Falls in Older People

See Appendix 3.

5.4 Hip Protectors

Ninety percent (90%) of hip fractures result from falls.⁶¹ Hip protectors reduce the impact on the hip during falls. The use of hip protectors in nursing home residents reduce the risk of hip fractures by up to 39%.^{62,63,64} However, compliance is a problem.⁶⁴

(Grade A, Level Ib)

5.5 Pharmacological agents

Hormone Therapy, Selective Estrogen Receptor Modulators (SERMs) and Bisphosphonates have been shown to be effective in prevention of osteoporosis. Vitamin D supplements reduce falls. For further details, please refer to Chapter 6.

6. MANAGEMENT OF POSTMENOPAUSAL OSTEOPOROSIS

The treatment interventions in FRAX have been partly based on cost-effectiveness, for which there is no Malaysian data. Notwithstanding that, we would propose using the National Osteoporosis Foundation's recommended treatment thresholds. We therefore suggest that postmenopausal women should be considered for treatment, if they had a previous low trauma hip, vertebral or wrist (colles') fracture, or a T-score ≤ -2.5 on DXA, after exclusion of secondary causes of osteoporosis. In patients with osteopenia, initiation of treatment is recommended with a fracture probability, based on the FRAX calculation, of more than 3% at 10 years for hip or 20% at 10 years for major osteoporosis-related fracture.

(Grade C, Level IV)

6.1 Hormone Therapy (HT)

HT is an effective treatment for women with moderate to severe menopausal symptoms and is most effective before the age of 60 years or within 10 years of the menopause.⁷⁷

HT can be considered as a first line treatment for prevention and treatment of osteoporosis in women below 60 years.⁷⁷ It increases lumbar spine BMD up to 7.6% and femoral neck BMD up to 4.5% over 3 years. It reduces the risk of spine, hip and other osteoporotic fractures by 33-40%.^{65,66}

(Grade A, Level Ib)

Initiating HT in women after 60 years for the sole purpose of prevention of osteoporotic fractures is not recommended.^{65,66,67}

(Grade A, Level 1b)

The protective effect of oestrogen on bone is seen with all forms of HT i.e. unopposed oestrogen, addition of progestin in women with intact uteri, different oestrogen formulations (conjugated equine oestrogen or oestradiol valerate), different routes of administration (oral or transdermal) and different patterns of administration (cyclic versus continuous).⁶⁸

(Grade B, Level 11b)

Low and ultra-low doses of HT have been shown to be bone sparing and prevent postmenopausal bone loss though fracture prevention data is unavailable.^{67, 68}

(Grade A, Level Ib)

The maximum protection of bone mass occurs when oestrogen therapy is begun soon after menopause and for as long as the HT is continued. The benefits of HT on bone mass and fracture reduction dissipates quickly after discontinuation of therapy.^{69,70}

(Grade A, Level 1b)

Initiation of HT in the younger, women who recently underwent menopause, of less than 60 years, has not been shown to increase the risk of cardiovascular events, stroke, venous thromboembolism and haemorrhagic strokes.^{71,72}

(Grade A, Level 1b)

Combined oestrogen and progestin appear to increase the risk of breast cancer after 3-5 years, while data on oestrogen only users do not show an increase, up to 7 years of use. This risk of breast cancer reduces when HT is stopped.^{73,74,75}

(Grade A, Level 1b)

The use, dose and duration of use of HT should be individualised and a risk - benefit assessment carried out annually while on treatment. A full gynaecological assessment is mandatory prior to starting HT and at regular intervals thereafter. Self breast examination is advised monthly and clinical breast examination at least annually. A mammogram should be carried out 1-2 yearly if the initial mammogram is normal.

Absolute contraindications for oestrogen use are undiagnosed vaginal bleeding, severe liver disease and a history of venous thromboembolism.

(Grade C, Level IV)

HT should be offered to all women with premature ovarian failure in view of the increased risk of osteoporosis, cardiovascular disease, urogenital atrophy and libido. HT is given till the normal age of menopause; continuation thereafter is made after a risk-benefit assessment.⁷⁶

(Grade C, Level IV)

Recommendations for HT

1. HT can be considered as a first line treatment for prevention and treatment of osteoporosis in women below 60 years. In this group of women, HT has not been shown to increase the risk of cardiovascular events, stroke, venous thromboembolism and haemorrhagic strokes
2. Initiating HT in women after 60 years for the sole purpose of prevention of osteoporotic fractures is not recommended
3. Combined oestrogen and progestin appear to increase the risk of breast cancer after 3-5 years, while data on estrogen only users do not show an increase up to 7 years of use
4. The use, dose and duration of HT should be individualized and a risk - benefit assessment should be carried out annually while on treatment

Table 12. Effective Bone Protective Doses of Estrogen^{67,68}

Type of oestrogen	Dose
Conjugated Equine Estrogen (CEE)	0.3, 0.625 mg
Estradiol Valerate	1.0, 2.0 mg
Transdermal estradiol	25 -100 ug
Micronised estradiol	0.5, 1.0 mg
Tibolone*	2.5 mg

*STEAR (Selective Tissue Estrogenic Activity Regulator)

6.2 Tibolone

Tibolone, a selective tissue estrogenic activity regulator (STEAR) is indicated for the relief of climacteric symptoms and prevention of post-menopausal osteoporosis. In older post-menopausal women above 60 years, tibolone at 1.25mg increases lumbar spine BMD by 6.6% and hip BMD by 2.8% with a corresponding decrease in vertebral fractures by 45% and non-vertebral fractures by 26%. There was a greater reduction in women with a pre-existent vertebral fracture.^{78,79}

In view of an increased risk of stroke, tibolone should not be used in older women (above 60 years) and in women with strong risk factors for stroke.⁷⁹

(Grade A, Level 1 b)

Though tibolone does not cause increased mammographic density, it is not recommended in women with a personal history of breast cancer and for long term use (above 5 years).^{79,80}

(Grade A, Level 1 b)

6.3 Selective Estrogen Receptor Modulators (SERMs)

Selective Estrogen Receptor Modulators (SERMs, e.g. raloxifene at 60 mg daily) improve and preserve bone density at both the spine (2.6%) and hip (2.1%) after 4 years.⁸¹ It has been shown to be beneficial in reducing new vertebral fracture risk by 69% in postmenopausal women with osteoporosis and 47% in postmenopausal women with osteopenia over 3 years.⁸⁴

Compared with placebo in postmenopausal women at average risk of breast cancer in the published osteoporosis trials, raloxifene reduces the risk of invasive breast cancer by 44-76%.^{82,83} Raloxifene has been shown to be as effective as tamoxifen in reducing the risk of invasive breast cancer and is thus indicated for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis.¹⁸¹

Raloxifene and estrogen are associated with a similar increased risk of venous thromboembolism (VTE). However, no cases of VTE were reported amongst healthy postmenopausal Asian women whilst on raloxifene.⁸⁵

Other side effects include hot flushes, which are more likely in the peri-menopausal period, and leg cramps.

(Grade A, Level 1b)

6.4 Bisphosphonates

Bisphosphonates are potent inhibitors of bone resorption.

6.4.1 Alendronate

Alendronate at 10 mg daily for 3 years increases lumbar spine BMD by up to 8.8% and femoral neck BMD by 5.9% compared to placebo.⁸⁷ The rate of new vertebral and hip fracture is reduced by 50% in women with⁸⁷ or without⁸⁸ prior fracture. Wrist fracture is reduced by 50% in patients with prior vertebral fracture⁸⁹. Fracture reduction is seen after 1 year of treatment.⁹⁰

Alendronate 70 mg weekly has similar efficacy to alendronate 10 mg daily in the treatment of postmenopausal osteoporosis.⁹⁰

Continuous use of alendronate, for up to 10 years, if clinically indicated, produces a sustained increase in BMD and 55% significant reduction in spine fracture with a good safety profile.^{91,92}

(Grade A, Level Ia)

6.4.2 Risedronate

Treatment with risedronate 5 mg daily for 3 years increases lumbar spine BMD by 6.4%⁹³ and femoral neck BMD by 3.4%⁹⁴ compared to placebo. This is associated with up to 49% reduction in new vertebral fracture in women with prior vertebral fractures⁹⁵ and 39% reduction in non-vertebral fractures.⁹⁶ Vertebral fracture risk reduction is seen after 6 months of therapy.⁹⁷ Reduction of hip fracture risk after 3 years was 40% in women with confirmed osteoporosis and 60% in women with at least one co-existing vertebral fracture.⁹⁴ Currently, the use of risedronate for up to 7 years, is safe and efficacious.⁹⁸ Risedronate 35 mg once weekly has similar efficacy to the 5 mg daily dosing.⁹⁷

(Grade A, Level Ia)

6.4.3 Ibandronate

Treatment with oral ibandronate 150 mg/month increases the lumbar spine BMD by 6.6% over 2 years in postmenopausal osteoporotic women without prior fracture compared to placebo.⁹⁹ Oral ibandronate 2.5 mg daily for 3 years reduces vertebral fracture by 62% in postmenopausal women with prevalent vertebral fracture.¹⁰⁰ The currently licensed ibandronate dose of 150 mg a month has been shown to be non-inferior to the 2.5 mg daily dose in terms of BMD gain and bone marker suppression.¹⁰¹ Pooled analysis showed significant reduction of non-vertebral fracture by 38-43% over 2 years.¹⁰²

(Grade A Level Ib)

6.4.4 Zoledronic acid

Treatment with zoledronic acid (5 mg by intravenous infusion over at least 15 minutes once yearly) in osteoporotic postmenopausal women reduces the incidence of vertebral fracture by 70% over 3 years with significant reduction seen by one year. Hip fracture is reduced by 41% and non vertebral fracture by 25% over 3 years.¹⁰³

(Grade A Level Ib)

Zoledronic acid yearly infusion is also indicated for the prevention of new clinical fractures in patients who recently (within 90 days) have had a low trauma hip fracture.¹⁰⁴ It has also been shown to be associated with a reduction in mortality.¹⁰⁴

Adverse effects of bisphosphonates

Two adverse effects have been noted in bisphosphonate therapy:

1. Atypical femoral shaft fractures
2. Osteonecrosis of the jaw (ONJ)

Atypical Femoral Shaft Fractures

Atypical femoral shaft fractures have been increasingly recognised in patients on long-term bisphosphonate therapy. The risk of atypical femoral shaft fracture appears to escalate with increase duration of bisphosphonate use. However, current evidence has not established a causal association between bisphosphonates and these atypical femoral shaft fractures.^{105,106}

The absolute risk of atypical fracture is low, ranging from 1.9-8.4/10,000 patient-years with average of 5.5/10,000 patient-years.¹⁰⁶ The benefits of bisphosphonate therapy, by reducing classical osteoporotic fracture, outweigh the rare risk of this fracture.^{105,106}

Osteonecrosis necrosis of the jaw (ONJ)

Osteonecrosis of the Jaw (ONJ) is defined as “exposed, non-vital bone involving maxillofacial structures, with delayed healing despite > 8 weeks of appropriate medical care.”¹⁰⁷ It is thought to be caused by trauma to dentoalveolar structures that have a limited capacity for bone healing.

The frequency of ONJ in osteoporotic patients is rare ranging from 0.01 - 0.04% (1 in 2,260 to 8,470)¹⁰⁸ patients to <1/100,000^{109,107} patient years for those on oral (mainly weekly) bisphosphonates. If extractions were carried out, the calculated frequency is 0.09 - 0.34% (1 in 296 to 1,130 cases).¹⁰⁷

However, it is more commonly seen in patients on oncological doses (high dose, IV) of bisphosphonates, used for treatment of cancer / who have bone metastases, who are immune suppressed / had radiation / infection / poor oral hygiene / have invasive dental procedures, where the incidence ranges from 4-13%.¹¹⁰

Other common side effects of oral bisphosphonates are gastro-intestinal, commonly nausea, although the actual incidence is low. Proper administration of bisphosphonates will reduce the small risk of oesophagitis or oesophageal ulceration. The evidence to date on possible association between oral bisphosphonates and oesophageal cancer is inconclusive.

For patients with upper gastrointestinal disease, risedronate may be better tolerated.¹¹¹ Intravenous zoledronic acid is another option.

Use of bisphosphonates in renal impairment / Chronic Kidney Disease (CKD)¹¹²

CKD Stages 1-3

Patients with CKD stages 1-3 and low T-scores or low trauma fractures, most likely have osteoporosis rather than renal bone disease. Treatment of osteoporosis does not differ from usual treatment for postmenopausal osteoporosis. Bisphosphonates can be used safely.

Caution is required when using intravenous bisphosphonates. Patients should be well hydrated, the infusion should be given slowly (>15 mins) and nephrotoxic drugs e.g. non-steroidal anti-inflammatory drugs (NSAIDs), should be avoided.

CKD Stages 4-5

Bisphosphonates are not recommended for patients with an estimated GFR < 30 ml/min (See Appendix 4).

Recommendations for the Use of Bisphosphonates

It is recommended to evaluate the efficacy of bisphosphonate therapy after 3-5 years¹⁷³

If a lack of efficacy is noted, i.e. significant deterioration of BMD, or recurrent low trauma fracture, re-evaluation is required to exclude the following:

1. Secondary causes of osteoporosis
2. Drug compliance

If the above have been excluded, bisphosphonates can either be continued or an alternative therapy can be considered (i.e. anabolic therapy)

When prescribing bisphosphonates for longer than 5 years, evaluation of the need for continued bisphosphonate therapy is recommended. In patients:

1. with low risk of fracture, consider a drug holiday
2. with evidence of atypical femoral shaft fracture, bisphosphonate therapy should be discontinued
3. with high risk of fracture, consider continuing bisphosphonate therapy up to 10 years⁹²

6.5 Recombinant human PTH 1-34 (r-PTH)

Recombinant human PTH 1-34 (r-PTH), teriparatide, is a potent anabolic agent. r-PTH is indicated for individuals with severe osteoporosis or osteoporosis not responsive to other anti-osteoporosis therapy.

Subcutaneously administered r-PTH at 20 micrograms 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. The rate of new vertebral and non-vertebral fracture is reduced by 65% and 53% respectively.¹¹³

Current recommendation for the treatment duration of r-PTH is up to 24 months.

(Grade A, Level Ib)

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 C, Level IV)

6.6 Strontium Ranelate

Strontium Ranelate reduces bone resorption while promoting bone formation.¹¹⁴

A pooled estimate showed a relative risk reduction of 37% for vertebral fracture^{114,116} and 14%^{115,116} for non-vertebral fracture. Efficacy for reduction of incident vertebral fractures was seen as early as 1 year (49% reduction). In a subgroup of high risk women (i.e. women aged >74year with a femoral neck BMD T-score <-3.0), the relative risk reduction of hip fracture was 36% (RR 0.64, 95% CI 0.41-0.99), which was borderline significant. This anti-fracture efficacy is sustained up to 10 years.¹¹⁷

(Grade A, Level 1b)

Caution is necessary when interpreting BMD change as the increased X-ray absorption of strontium compared to calcium leads to an amplification of BMD measurement by DXA. An increase in lumbar spine BMD over a 2 year treatment period is 11.29g/cm² (CI 10.22 - 12.37) when not adjusted for strontium but is in fact, 5.44g/cm², (CI 3.41 - 7.46) when adjusted for strontium content. At the femoral neck over a 2 year period, there is an increase of 5.73g/cm² (CI 5.15 - 6.32).¹¹⁸

Side effects include diarrhoea and Drug Rash with Eosinophilia Systemic Symptoms (DRESS).

Based on a recent review by the European Medicines Agency (EMA) in 2014 assessing the increased signal for non-fatal myocardial infarctions in the clinical trials, they recommended that strontium is indicated for the treatment of severe/established osteoporosis in postmenopausal women at high risk of fracture to reduce the risk of vertebral and hip fracture, and severe/established osteoporosis in men at increased risk of fracture. It should only be used for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance. The decision to prescribe strontium should be based on an assessment of the individual's patient's overall risk.¹⁸²

If the patient has any of the criteria below, do not prescribe strontium¹⁸⁰:

- Established, current, or past history of ischaemic heart disease, peripheral vascular disease and/or cerebrovascular disease
- Uncontrolled hypertension
- Current or previous Venous Thromboembolic Events (VTE), including deep vein thrombosis and pulmonary embolism
- Temporary or permanent immobilization due to e.g. postsurgical recovery or prolonged bed rest
- Hypersensitivity to strontium ranelate or any of its excipients

6.7 Denosumab

Denosumab is a human monoclonal antibody (IgG₂) that inhibits the formation, function and survival of osteoclast by preventing RANK (receptor activator of nuclear factor kappa-B) ligand from activating its only receptor, RANK, thus reducing bone resorption.¹¹⁹

Over 3 years, denosumab 60mg given 6 monthly subcutaneously, significantly increased BMD by 9.2% at the lumbar spine, 6.0% at the total hip, 4.8% at the femoral neck and 3.5% at the distal 1/3 radius, as compared to placebo.¹²⁰ It significantly reduced the risk of new vertebral fractures by 68%, hip fractures by 40% and non-vertebral fractures by 20%.¹²⁰

(Grade A, Level 1b)

6.8 Calcium

In established osteoporosis, calcium supplementation alone is not adequate for fracture prevention. However, calcium supplementation is necessary for optimal response to other treatment modalities. (see section 5.1.1)

6.9 Vitamin D

Vitamin D supplementation at 800 IU/day in combination with calcium has been shown to reduce fracture in elderly populations with vitamin D insufficiency.^{50,118}

(Level Ib)

In most of the recent osteoporosis trials, active therapies have demonstrated significantly increased bone density and greater fracture reduction, despite calcium and vitamin D in the placebo arm. Therefore, calcium with vitamin D alone is generally considered inadequate for the treatment of osteoporosis, and should usually be prescribed together with other active osteoporosis therapies.

(Grade C, Level IV)

In a global epidemiological study of postmenopausal women (which included Malaysian subjects), 61% were found to be vitamin D insufficient (<30 ng/mL).¹⁸³ Fifty percent of the Malaysian cohort were vitamin D insufficient. Therefore, we recommend vitamin D supplementation of 800-2000 IU daily, in osteoporotic women, in addition to other active osteoporosis treatments.

(Grade C, Level IV)

6.10 Activated Vitamin D

Activated Vitamin D (calcitriol 0.25 µg bd, alfacalcidol 1 µg od) has been demonstrated to increase BMD in those with established osteoporosis¹²¹ and reduce vertebral (47%) and non-vertebral fractures (66%).^{122,123,124} The reduction in fracture risk is in the spine and in those with mild to moderate osteoporosis.¹²⁵

(Level Ib)

All patients on activated Vitamin D should avoid taking more than 800 mg of calcium supplements to reduce the risk of hypercalcemia and renal stone disease. Serum and urinary calcium should be monitored periodically, 6 weeks after initiation of therapy and at 3 to 6 monthly intervals thereafter.¹⁷

(Grade C, Level IV)

6.11 Calcitonin

Calcitonin has limited efficacy in the treatment of postmenopausal osteoporosis. It is no longer recommended for use in osteoporosis because of an association between calcitonin use and a 0.7-2.4% absolute increased risk of various cancers.¹²⁶

(Grade A, Level Ib)

Side effects of calcitonin include nausea, flushing, vomiting and nasal irritation.

The suggested pathway for the treatment of postmenopausal osteoporosis shown in the Figure 1 algorithm.

Overall recommendation for the treatment of postmenopausal osteoporosis

The choice of drug for established osteoporosis, especially those with previous fracture must be an agent shown not only to increase BMD, but also shown to reduce fracture both at the spine and hip.

(Grade A, Level Ia)

7. MANAGEMENT OF OSTEOPOROTIC FRACTURES

The goals of treatment are early mobilisation and a return to normal activities. Conservative management of hip fractures is discouraged because it places the patient at risk of respiratory problems, thromboembolic disease, pressure ulcers and further bone loss. These patients are best treated by early surgical intervention.¹²⁸

Vertebral compression fractures are associated with increased morbidity and mortality.¹²⁹ The majority of osteoporotic vertebral fractures are stable. Operative intervention is indicated for those fractures complicated by spinal cord or nerve root compression. Surgery may be required for those with chronic backache and progressive spinal deformities.

(Grade C, Level IV)

Symptomatic relief of spinal pain is often difficult to achieve. Morphine and other potent analgesics may be required. Calcitonin is a useful adjunctive analgesic agent.¹²⁷

(Grade A, Level Ib)

Significant relief may be achieved through physiotherapy, activity modification and bracing (e.g. lumbar corset).

(Grade A, Level Ib)

Vertebroplasty, a percutaneous injection of cement augmentation of the vertebra has produced quick and significant relief of backache in selected cases.^{130,131}

(Grade B, Level III)

A recent randomised controlled study showed that vertebroplasty cement augmentation of the acutely fractured vertebrae may be only as effective as conservative treatment.¹³²

(Grade A, Level 1b)

Adequate calcium¹²², vitamin D⁶ **(Grade A, Level Ib)** and protein intake aids fracture healing.¹²³ **(Grade B, Level III)** All patients with osteoporotic fractures are at high risk for the development of further fractures. They should receive active management for osteoporosis and advised regarding prevention of falls.

(Grade A, Level Ia)

Recommendations

- Conservative management of an acute vertebral fracture is the preferred treatment modality. Vertebroplasty may be used for certain patients with severe pain and restricted mobility
- Hip fractures should be surgically managed promptly to allow early ambulation. Spine and wrist fractures may need operative intervention

(Grade C, Level IV)

8. SECONDARY OSTEOPOROSIS

8.1 Glucocorticoid-Induced Osteoporosis (GIOP)

Osteoporosis is a major complication of glucocorticoid therapy. Patients on glucocorticoid therapy are at increased risk of sustaining fractures over and above that of the underlying disorder.

(Level Ia)

Bone loss occurs most rapidly in the first 6-12 months of oral glucocorticoid therapy.^{124,125}

(Level III)

There is an increase in fracture risk that appears within 3 to 6 months of starting glucocorticoids.¹³³ Fractures occur in patients with GIOP at a higher BMD compared to post-menopausal osteoporosis.

(Level Ia)

Prednisolone \geq 5 mg daily or its equivalent, for more than 3 months is associated with osteoporosis.^{16,133}

(Grade B, Level III)

However, higher doses of glucocorticoids for a shorter duration may also carry the same risk.

(Level IV)

Standard doses of inhaled or topical glucocorticoid use have not been shown to adversely affect BMD. Inhaled high potency glucocorticoid over an extended period of 7 years have been associated with significant bone loss.¹³⁴

(Level IIa)

8.1.1 Diagnosis

The use of BMD measurement for the diagnosis of GIOP is not crucial, but may be useful in the monitoring of therapy. DXA measurement at the hip provides the best assessment of fracture risk as degenerative changes at the spine may cause falsely high BMD result.¹³⁵ Diagnostic thresholds in GIOP have not been established for peripheral densitometry using either DXA or ultrasound, which therefore should not be used for assessment or monitoring.^{135,136}

The use of FRAX is recommended to categorise patients into low, medium and high risk groups with respect to the 10-year risk of fracture.

In postmenopausal women and men over 50 years old with low risk of fracture, treatment is recommended when prednisolone (or its equivalent) ≥ 7.5 mg daily is taken for more than 3 months. In medium risk patients, treatment is recommended at any dose of glucocorticoid when taken for more than 3 months. In high risk patients, treatment is suggested for any dose of glucocorticoid taken for any length of time.

For premenopausal women of non-childbearing potential and men under 50 years old with a prevalent osteoporotic fracture, treatment is recommended if prednisolone ≥ 5 mg daily is given for > 1 month. For premenopausal women of childbearing potential, treatment is recommended when prednisolone ≥ 7.5 mg daily is given for > 3 months.^{3, 179} (See algorithms: Figure 3, page 13 and Figure 4, page 14)

There has been a recommendation that the FRAX risk estimates are adjusted according to the daily dose of glucocorticoids. For low-dose exposure (< 2.5 mg daily of prednisolone or equivalent), the probability of a major fracture is decreased by about 20% depending on age. For medium doses (2.5–7.5 mg daily), the unadjusted FRAX value can be used. For high doses (> 7.5 mg daily), probabilities can be upward revised by about 15%.¹³⁷

8.1.2 Management

8.1.2.1 General measures include:

- a) Prescribing the lowest effective dose of glucocorticoid for disease control¹³⁸
- b) The use of alternative route of administration¹³⁸ (e.g. inhaled steroids in asthma)
- c) Consider the use of steroid- sparing agents
- d) Modification of lifestyle - adequate calcium intake, adequate mobilisation, regular exercise and prevention of falls

(Grade C, Level IV)

8.1.2.2 Specific measures:

In hypogonadal states, replacement therapy with sex steroids should be considered.

(Grade A, Level Ib)

All patients on glucocorticoids should be supplemented with calcium and vitamin D (1000-1500 mg/day and 800 IU/day respectively).¹³⁹

(Grade A, Level Ia)

Drugs found to be effective in management of GIOP are shown in Table 13.

Table 13: Grades of Recommendation for Preventive and Therapeutic Interventions in Glucocorticoid-induced Osteoporosis

Drug	Primary Prevention	Secondary Prevention/ Treatment	Vertebral fracture reduction	Reference
Alendronate 10mg od	A	A	A	140,141
Alendronate 70mg/wk	A	A	ND	142
Alfacalcidol	A	A	ND	143,144
Calcitriol	A	ND	ND	146
Calcium & Vitamin D	ND	A	ND	147
Etidronate	A	A	A	148,149
Hormone Therapy (in females)	ND	A	ND	150
Pamidronate	A	A	ND	151,152
Parathyroid Hormone	ND	A	A	153
Risedronate	A	A	A	154,155
Testosterone (in males)	ND	A	ND	156
Zoledronate	A	A	ND	157

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

In a study comparing alendronate, vitamin D and calcitriol, alendronate increased lumbar spine BMD by 5.9% over 2 years, compared to 0.5% and 0.7% loss on vitamin D and calcitriol respectively. There was no difference at the femoral neck.¹⁵⁸ In a prevention study comparing alendronate and alfacalcidol over 18 months, patients on alendronate maintained or improved their lumbar spine and femoral neck BMD compared to BMD loss in the alfacalcidol group.¹⁵⁹ IV zoledronate produced a better gain in lumbar spine and femoral neck BMD compared to oral risedronate over 1 year.¹⁵⁷ Teriparatide led to a better gain in lumbar spine and femoral neck BMD compared to alendronate over 3 years.¹⁵³ Alendronate and risedronate reduced vertebral fractures in patients on glucocorticoid therapy.^{141,155}

In patients on glucocorticoids with osteoporotic fractures or confirmed osteoporosis on DXA, bisphosphonates are the first-line treatment.

(Grade A, Level Ib)

The treatment pathways for postmenopausal women and men over the age of 50 with GIOP are shown in Figure 3 (page 13). For premenopausal women and men below the age of 50, the suggested pathway is shown in Figure 4 (page 14).

Treatment should be continued as long as the patients are on glucocorticoids.¹⁶ Upon discontinuation of glucocorticoids, treatment should be continued as in non-glucocorticoid osteoporosis for those with established or high risk of osteoporosis.

(Grade C, Level IV)

Table 14: Clinical factors that may shift an individual to a greater risk category for glucocorticoid-induced osteoporosis

Low body mass index

Parental history of hip fracture

Current smoking

≥ 3 alcoholic drinks per day

Higher daily glucocorticoid dose

Higher cumulative glucocorticoid usage

Intravenous pulse glucocorticoid usage

Declining central bone mineral density measurement that exceeds the least significant change

8.2 Renal Osteodystrophy

Renal osteodystrophy is a common complication of renal disease particularly those on dialysis. The severity increases with duration of dialysis. The mainstay of treatment is to address the metabolic abnormalities associated with renal impairment, namely correction of acidosis, hyperphosphataemia and hypocalcaemia.

(Grade C, Level IV)

8.3 Amenorrhoea

Extreme physical activity, 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.

(Grade B, Level III)

8.4 Drugs

Drugs that can cause alteration in bone metabolism include anti-convulsants, 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 should be considered.

(Grade C, Level IV)

8.5 Other Secondary Causes of Osteoporosis

Other causes of secondary osteoporosis shown in Table 5 should be assessed and treated appropriately.

9. OSTEOPOROSIS IN MEN

Osteoporosis is increasingly recognised in older men, with a life-time fracture risk in 50 year old men of 20%. Men account for up to 30% of hip fractures and 42% of clinical vertebral fractures.¹⁶⁰

(Grade C, Level IV)

Fifty to sixty percent of cases are due to secondary causes such as hypogonadism (including androgen deprivation therapy), excess alcohol intake, hyperparathyroidism, intestinal disorders, malignancies, glucocorticoid therapy and immobilisation. For every one SD reduction in age-matched mean BMD (Z score), fracture risk increases two-fold.¹⁶¹

(Grade B, Level III)

9.1 Treatment

The management consists of identifying and treating underlying causes. Androgen treatment is beneficial in hypogonadal men.¹⁶² It may be of some benefit in eugonadal osteoporotic men.^{162,163}

Once weekly alendronate¹⁶⁰, once weekly risedronate¹⁶⁴ and once monthly ibandronate¹⁷⁸ have been shown to increase BMD in the lumbar spine and femoral neck in men with osteoporosis (T-score -2.0). Alendronate treatment was shown to reduce radiographic vertebral fracture over 2 years.^{160,165} Similarly, risedronate treatment resulted in a decrease of new vertebral fracture over 2 years.¹⁶⁶ A once yearly infusion of IV zoledronate has been shown to improve BMD similar to once weekly alendronate over 2 years.¹⁶⁷

Teriparatide (rPTH)¹⁶⁸ has been shown to be effective in the treatment of osteoporosis in men. No fracture data is available in the teriparatide study.¹⁶⁹

(Grade A, Level Ib)

Denosumab treatment for 1 year has been shown to increase BMD at the lumbar spine, femoral neck, trochanter and distal one third radius in men with low bone mass.¹⁸⁴

(Grade A, Level Ib)

Strontium ranelate treatment for 2 years has been shown to increase BMD at the lumbar spine, femoral neck and total hip in men with osteoporosis.¹⁸⁵

(Grade A, Level Ib)

The suggested pathway for the assessment and treatment of men with osteoporosis is shown in Figure 2.

Recommendation

Men with osteoporosis should be investigated for secondary causes. Bisphosphonates, and PTH, denosumab and strontium have been shown to be effective, and androgen is useful in hypogonadal men.

(Grade A, Level Ib)

10. Implementing The Guidance

Although there is no health economic data with regards to the benefits of treating osteoporosis from Malaysia, studies from the United States (US) and Europe have shown that there is a personal and societal benefit to treating patients with osteoporosis. In Europe, osteoporotic fractures are associated with more disability compared to rheumatoid arthritis, hypertensive heart disease and breast cancer.¹⁷⁴ Furthermore, the rate of osteoporotic hip fractures has been shown to be increasing in Asia¹⁷⁵ with associated increased costs.

In addition, the societal cost of osteoporosis has been increasing. In 1995, the cost of osteoporotic fracture care in the US was US\$13.8 billion and the proportion spent on hospital, long term and outpatient care was similar.¹⁷⁶ By 2005, the total annual cost of osteoporosis fractures in the US is estimated to be US\$16.9 billion of which 57% was spent on hospital in-patient care, 30% on long term institution care and 13% on outpatient care.¹⁷⁷

10.1 Existing Facilitators and Barriers

Existing facilitators for application of the recommendations in the Clinical Guidance include:

- a) Extensive network of rheumatologists, orthopaedic surgeons and endocrinologists nationwide that can provide clinical input in the management of osteoporosis
- b) The availability of bone density measurement with DXA in the majority of General Hospitals in Malaysia (public sector)
- c) The availability of the Clinical Guidance in both hard copy for medical and paramedical personnel [available from Malaysian Osteoporosis Society (MOS) and via Continuing Medical Education programmes on the Guidance run by MOS] and soft copy [on the websites of Ministry of Health, Academy of Medicine, MOS and Malaysian Society of Rheumatology]

Existing barriers for its application are:

- a) Early recognition of osteoporosis at the primary care level
- b) Apart from the Klang Valley area, there is limited availability of DXA outside the capital towns in each state
- c) The lack of availability of the full range of medications stated in the Clinical Guidance in the public hospitals

10.2 Potential Resource Implications

To ensure that the Clinical Guidance is used, the following factors should be in place, which have resource implications:

- a) Provide training for primary care physicians to be able to recognise osteoporosis at the primary care level (primary prevention)
- b) Provide training to all doctors (both at primary and secondary care levels) to recognise and treat osteoporosis following an osteoporotic fracture (secondary prevention)

- c) Ensure that the screening tools e.g. OSTA are readily available in Health Clinics and primary care clinics at major population centres
- d) Ensure that there is easy availability of DXA machines, especially outside the Klang Valley. This would require both investment in purchasing the machine as well as training of the DXA technicians performing the scans. These DXA technicians will continue to require regular continuing professional education to keep updated
- e) Ensure that a mechanism exists by which primary care physicians/family medicine specialists/general practitioners can directly refer patients for DXA scans to the General Hospitals
- f) Ensure availability of the drugs mentioned in the Clinical Guidance in the public as well as private hospitals

11. 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.

The proposed Clinical Audit would be:

$$\text{Percentage of patients with low trauma/osteoporotic hip fractures on osteoporosis treatment post-hip arthroplasty} = \frac{\text{Number of patient on osteoporosis treatment post-hip arthroplasty}}{\text{Total number of patients with low trauma/osteoporotic hip fractures}} \times 100\%$$

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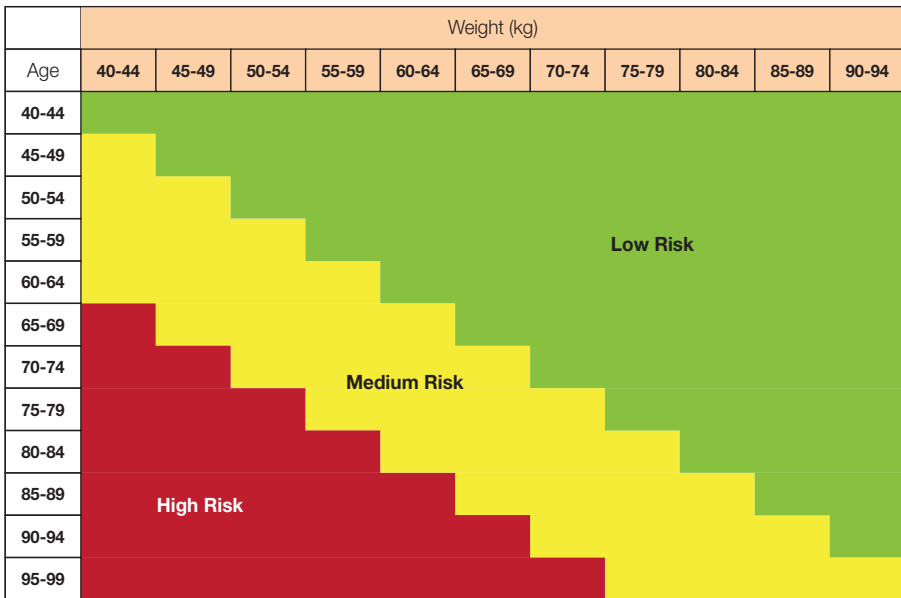
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14. Appendix 1

Osteoporosis Self-Assessment Tool for Asians (OSTA)



HIGH RISK
(61% risk of osteoporosis)



Measure BMD#, if possible
Consider pharmacologic
treatment even if BMD is not available¹⁷⁰

MEDIUM RISK
(15% risk of osteoporosis)



Measure BMD#, and consider
pharmacologic treatment
if BMD is low¹⁷⁰

LOW RISK
(3% risk of osteoporosis)



BMD, measurement is probably
not necessary unless other risk
factors are present¹⁷⁰

If your patient is in the yellow or red region of the chart above, her risk of osteoporosis is increased.

Note: Patients who have already had a non-traumatic fracture after menopause, have approximately twice the risk of future fractures regardless of their age, weight, or BMD, and should be considered for treatment.¹⁶⁵ The risk of future fractures is further increased if the patient also has low BMD.¹⁶⁵

Other factors may increase risk regardless of her current age and weight

* Important risk factors for accelerated bone loss include corticosteroid use (losses increase with dose and duration), hypogonadism (including menopause), and immobilization (bedridden, casted fractures, wheelchair-bound, etc.)¹⁷¹

BMD = Bone Mineral Density

Appendix 2

Calcium Content of Some Common Foods³⁴

Food	Calcium content (mg)
1 glass of high calcium milk (200 ml)	500
1 glass of skimmed milk (200 ml)	250
1 glass of full cream milk (200 ml)	220
1 cup of yoghurt (150 g)	200
1 piece tofu (150 g)	200
1/2 cup of yellow dhal (100 g)	170
1 cup of spinach (56 g)	160
1 cup of ice-cream (156 g)	150
1 cup watercress (sai-yong choy) (50 g)	100
1 piece of cheddar cheese (20 g)	100
1 cup of mussels (160 g)	100
1/2 cup of ikan bilis (dried without head & entrails) (20 g)	100
1 piece of canned sardine (40g)	100
1 cup of baked bean (240 g)	100
1 cup of mustard green (sawi), cekur manis, kai lan or pucuk ubi kayu (50 - 80 g)	100
1 piece of tempeh (70 g)	50
1 cup of soyabean milk (200 ml)	40
1 cup of broccoli (95 g)	40
10 almonds (15 g)	30
* 1 cup = 200 ml	

Appendix 3

Evidence for the prevention of falls in older people

Statement	Falls fracture reduction	Strength of evidence
Individually tailored exercise programmes administered by qualified professionals in selected community-living high risk group	Reduce falls	2
Exercise programmes in a selected community living group with mild deficits in strength and balance	Reduce falls	3
Exercise classes, where the exercise is based on Tai Chi forms, with individual tuition with older people	Reduce falls	2
Programmes based on multiple risk factor assessment and tailored intervention (most of which include some form of exercise)	Reduce falls	1
Attention to postural hypotension, number of medications, balance, transfers and gait	Reduce falls	2
Identification of patients who attend accident & emergency because they have fallen with subsequent medical and occupational therapy assessment, with referral and follow-up	Reduce falls	2
Assessment of residents after falling with recommendations for specific preventive measures	Reduce falls	1
Hip protectors in nursing home residents	Prevent hip fractures	2

Adapted from Cryer C et al. London: Alliance for Better Bone Health, 2001¹⁷²

Evidence grading:

- 1 – Consistent findings in multiple randomized controlled trials (RCTs) or meta-analysis
- 2 – Single RCT or weak inconsistent findings in multiple RCTs
- 3 – Limited scientific evidence, cohort studies, flawed RCTs, panel consensus

Appendix 4

Chronic kidney disease – Stages

Stages 1	GFR 80+ ml/min
Stages 2	GFR 80-60 ml/min
Stages 3	GFR 60-30 ml/min
Stages 4	GFR 30-15 ml/min
Stages 5	GFR <15 ml/min or ESRD / dialysis

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