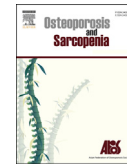


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Review article

# A summary of the Malaysian Clinical Guidance on the management of postmenopausal and male osteoporosis, 2015<sup>☆</sup>

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## Abstract

**Aim:** This Clinical Guidance is aimed to help practitioners assess, diagnose and manage their patients with osteoporosis (OP), using the best available evidence.

**Methods:** A literature search using PubMed (MEDLINE) and The Cochrane Library identified all relevant articles on OP and its assessment, diagnosis and treatment, from 2011, to update from the 2012 edition. The studies were assessed and the level of evidence assigned. For each statement, studies with the highest level of evidence were used to frame the recommendation.

**Results:** This article summarizes the diagnostic and treatment pathways for postmenopausal and male OP, while addressing the risk-benefit ratio for OP treatment. Recognising the limitation of only depending on bone mineral density in assessing fracture risk, a move to assess 10 year fracture risk using tools such as FRAX, is recommended as a guide to decision-making on when to start treatment. A re-evaluation was done of the position of calcium supplementation and on the importance of vitamin D. There has been concern about the potential adverse effects of the long-term usage of bisphosphonates, which have been discussed fully. Algorithms for the management of postmenopausal and male OP have been updated.

**Conclusions:** Adequate intake of calcium (1000 mg from both diet and supplements) and vitamin D (800 IU) daily remain important adjuncts in the treatment of OP. However, in confirmed OP, pharmacological therapy with anti-resorptives is the mainstay of treatment in both men and postmenopausal women. Patients need to be regularly assessed while on medication and treatment adjusted as appropriate.

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**Keywords:** Bisphosphonates; Calcium; Guidelines; Malaysia; Osteoporosis

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## 1. Introduction

Osteoporosis (OP) is a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [1]. Epidemiological studies have estimated that there would be an exponential increase in the incidence of osteoporotic fractures in Asia, so that by 2050, 50% of all hip fractures would occur in this region [2]. In Malaysia, in 1997, the incidence of hip fracture among individuals above 50 years of age was 90 per 100,000 population [3]. The incidence increased with age; in the 50–54 year olds, the incidence was 10 per 100,000, rising to 510 per 100,000 in those over 75 years old [3]. Malaysia still has a predominantly young population, with only 5.5% (~1.6 million) of its estimated 30 million populace above the age of 65 years. However, the life expectancy of Malaysians is increasing; it is 77.4 years for women and 72.5 years for men. With this ageing population, the burden of OP is expected to continue to rise in Malaysia.

The Malaysian Osteoporosis Society (MOS) had previously published Clinical Practice Guidelines in the Management of OP in 2001, 2006 and 2012, which aimed at providing a framework to assist doctors in the diagnosis and management of osteoporosis without restricting the physician's individual judgement. Following the 2012 edition, there were further data and studies, in the controversial area of calcium supplementation, bisphosphonate side effects (atypical femoral fractures and osteonecrosis of the jaw), and the place of hormone replacement therapy and strontium in the OP therapeutic armamentarium. Although other guidelines are available, this guidance was written in the context of a developing country such as Malaysia, taking into account the healthcare resources available locally. This guidance provides a review of the therapeutic agents available for the treatment of osteoporosis, with the aim of reducing fracture, and its accompanying morbidity and mortality.

## 2. Methods

The previous Clinical Practice Guidelines published in 2012 was used as the baseline. To update the document, a

Table 1  
Risk Factors for Osteoporosis and Fracture [Adapted from reference 6]

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. Alcohol intake of more than 3 units daily
5. Family history of osteoporosis or fracture in first degree relative	5. Caffeine intake of more than 330 mg daily (more than 3 cups daily)
6. Personal history of fracture as an adult	6. Low body weight (BMI < 19 kg/m <sup>2</sup> )
	7. Estrogen deficiency
	8. Frequent falls

systematic review and literature search by the members of the Working Group, using PubMed (MEDLINE) and The Cochrane Library, identified all relevant articles on OP and its assessment, diagnosis and treatment, from 2011 to 2015. The date 2011 rather than 2012 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 [4] (Appendix 1). 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 [5] (Appendix 1).

## 3. Results and discussion

### 3.1. The diagnosis of OP

The traditional risk factors, as shown in Table 1 (adapted from Ref. [6]), are still useful in identifying subjects at risk of OP and fracture (case finding) (*Grade C, Level IV*). The Osteoporosis Self-Assessment Tool for Asians (OSTA) is a simple table based on age and weight that can identify women who may be at high risk of OP who then may require a bone mineral density (BMD) measurement [7] (*Grade B, Level III*). The best method of assessing BMD is using dual-energy x-ray absorptiometry (DXA) at the lumbar spine and hip. General screening of the population is not recommended; the exceptions being women over the age of 65 and men over the age of

Table 2  
Indications for BMD Measurement<sup>a</sup>

- All women aged 65 and above and men aged 70 and above [8]
- Presence of strong risk factors
  - Estrogen deficiency
    - Premature menopause (<45 years of age) including surgical menopause
    - Prolonged secondary amenorrhoea
    - Hypogonadism
  - Glucocorticoid therapy
  - Maternal family history of hip fracture
  - Low body mass index (<19 kg/m<sup>2</sup>)
  - Other conditions associated with osteoporosis
    - Anorexia nervosa
    - Malabsorption
    - Hyperparathyroidism
    - Hyperthyroidism
    - Prolonged immobilisation
    - Cushing's syndrome
    - Post-bariatric surgical bypass
    - Drugs (e.g. aromatase inhibitors, GnRH agonists)
- Radiological osteopenia and/or vertebral deformity
- Previous low trauma fractures of hip, spine and/or wrist
- Loss of height, thoracic kyphosis
- Low weight for age (OSTA<sup>b</sup>) for postmenopausal women [7] (Appendix 2)

<sup>a</sup> BMD should only be measured in subjects who are willing to consider available interventions.

<sup>b</sup> OSTA = Osteoporosis Self-assessment Tool for Asians.

70 [8] (Grade C, Level IV). Table 2 shows the indications for BMD measurement.

Based on the World Health Organisation working group, OP can be diagnosed when the BMD value is 2.5 SD or more below the young adult mean (T-score  $\leq -2.5$ ), using a central DXA measurement, and/or in the presence of a fragility (low trauma) fracture [9]. Due to degenerative changes at the spine with ageing, the WHO international reference standard for osteoporosis diagnosis is a T-score of  $-2.5$  or less at the femoral neck [8]. When a patient presents with a low trauma fracture, OP is a presumptive diagnosis. BMD measurement with DXA is advised. However, in the absence of this facility, treatment should still be initiated (Grade C, Level IV).

Quantitative ultrasound (QUS) at the heel can predict fragility fracture in postmenopausal women (hip, vertebral and global fracture risk) and men over the age of 65 (hip and all non-vertebral fractures) independently of central DXA BMD [8] (Level III). It should not be used for the diagnosis of OP or for monitoring treatment effects. Patients with low QUS results should be referred for BMD measurement (Grade C, Level IV).

Bone turnover markers cannot be used for the diagnosis of OP. However, they can provide additional information on fracture risk and can be used to assess compliance with treatment [10]. The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommend that a marker of bone formation (serum procollagen type I N propeptide, s-P1NP) and a marker of bone resorption (serum C-terminal telopeptide of type I collagen, s-CTX) be used as reference markers for clinical studies [10] (Grade B, Level III).

### 3.2. Assessing OP and fracture risk

Initial investigations in a patient with OP would include a full blood count and ESR, serum calcium and phosphate, albumin, alkaline phosphatase, renal and thyroid function. Tests for testosterone, FSH, LH, urine Bence Jones protein and serum protein electrophoresis can be done where appropriate (Grade C, Level IV).

Until recently, treatment thresholds for OP have been based on BMD/T-score or the presence of a fragility fracture. Risk factors were used to help identify people that require BMD measurement. However, it became apparent that presence of several of the risk factors used to trigger sending the patient for a BMD test is associated with a fracture risk greater than can be accounted for by BMD alone [11] (Level III). Thus, a full OP assessment should try to integrate the clinical risk factors and BMD to give a better fracture risk assessment than either alone. The Fracture Risk Assessment Tool (FRAX) is one such assessment tool that is available.

FRAX estimates the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus or forearm) for untreated patients between the ages 40–90 years using clinical risk factors which include an individual's age, gender, weight, height, prior fracture, parental history of hip fracture, smoking, long-term use of

glucocorticoids, rheumatoid arthritis and alcohol consumption [12,13]. One advantage of FRAX is that BMD is not necessary for calculation 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 [12,13] (Grade B, Level III).

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, Singapore Malay, Singapore Indian) until local data is available (Grade C, Level IV).

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  $\leq -2.5$  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 [14] (Grade C, Level IV).

The interventions that have been shown to be useful in the prevention of OP are shown in Table 3.

### 3.3. Treatment of OP

The aim of treating OP is to reduce future fractures, not just to improve BMD. Patients found to have OP should have a careful assessment to exclude secondary causes of OP, which should then be treated in their own right (Grade C, Level IV). General management includes assessment of the risk of falls and their prevention [15,16] (Grade A, Level Ia). An adequate calcium and vitamin D intake is recommended (see discussion below). The major pharmacological interventions available in Malaysia are the bisphosphonates, strontium ranelate, denosumab, teriparatide, raloxifene and hormone therapy (HT), all

Table 3  
Efficacy of the interventions for the prevention of osteoporosis

Intervention	BMD improvement	Decrease vertebral fracture rate	Decrease hip fracture rate
Exercise	A [39]	–	–
Calcium and Vitamin D supplements	A [40]	A [40]	A [40]
Dietary calcium intake	B [41]	–	–
Smoking cessation	C	–	–
Reduced alcohol consumption	C	–	–
Prevention of falls	–	–	B [42]
Estrogen	A [43]	A [43]	A [43]
Raloxifene	A [44]	A [45]	–
Alendronate	A [46]	A [47]	–
Tibolone	A [48]	A [48]	–

Table 4

Efficacy of treatments available for osteoporosis. All the below treatments have been shown in randomised controlled trials to increase bone mineral density (Grade A)

Intervention	Decrease vertebral fracture rate	Decrease hip fracture rate
Alendronate	A [49,50]	A [49,50]
Ibandronate	<sup>a</sup> A [51]	–
Risedronate	A [52,53]	A [54]
Zoledronate	A [55]	A [55]
Strontium Ranelate	A [56]	A [57]
Denosumab	A [58]	A [58]
r-PTH (teriparatide)	A [59]	–
Hormone Therapy	A [43]	A [43]
Tibolone	A [48]	–
Raloxifene	A [60]	–
Calcitriol/Alfacalcidol	A [61,62]	–
Calcium ± vitamin D	A [40]	A [63]

Grades corresponds to the Grades of Recommendation as in Appendix 1.

<sup>a</sup> The vertebral fracture reduction was shown with the 2.5 mg daily oral dosing. The currently licenced ibandronate dose of 150 mg/month, has been shown to be non-inferior to the 2.5 mg daily dose in terms of BMD gain and bone marker suppression [64].

of which increase BMD and reduce vertebral fractures when given with calcium and vitamin D (*Level Ia, Ib*). However, not all of them reduce hip fracture (*Levels Ia, Ib*). A summary of their efficacy is shown in Table 4.

Since the last edition, there has been a re-evaluation in the role of HT and strontium ranelate in OP treatment. HT can be considered as a first line treatment for prevention and treatment of OP in women below 60 years [17]. Initiating HT in women after 60 years for the sole purpose of prevention of osteoporotic fractures is not recommended [18]. Following a review by the European Medicines Agency in 2014, assessing the increased signal for non-fatal myocardial infarctions in the clinical trials, they recommended that strontium ranelate should only be used for patients with OP in whom treatment with other medicinal products approved for the treatment of OP is not possible [19]. Additional contra-indications for the prescription of strontium now include established, current, or past history of ischaemic heart disease, peripheral vascular disease and/or cerebrovascular disease and uncontrolled hypertension [19].

Furthermore, the safety of calcium and long term bisphosphonate usage remain unresolved which will be discussed further in the following sections.

### 3.3.1. Calcium

For Malaysian women 50 years old or older, the recommended daily calcium intake is 1,000 mg [20] (*Grade C, Level IV*). This represents the total calcium intake (diet plus calcium supplements, if applicable). Table 5 lists the calcium content of some of the foods commonly found in Malaysia and other parts of Asia, which may be relevant when advising Asian patients.

Recent conflicting data suggest that excessive calcium supplementation is associated with an increase in myocardial

Table 5

Calcium content of some common Malaysian foods [65]

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 of 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 of 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 anchovies (ikan bilis) (dried without head & entrails) (20 g)	100
1 piece of canned sardine (40 g)	100
1 cup of baked beans (240 g)	100
1 cup of leafy green vegetables (e.g. 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.

infarction (MI) and cardiovascular events [21,22]. A meta-analysis suggested that calcium supplements (on average 1,000 mg daily) taken without vitamin D increase the risk of MI, relative risk 1.27 (95% CI 1.01–1.59) [21] (*Level Ia*). Another meta-analysis of calcium or calcium and vitamin D showed an increase in the relative risk of MI of 1.24 (1.07–1.45),  $p = 0.004$  [22] (*Level Ia*). In both the meta-analyses, the average calcium intake, both from dietary sources and supplements, was 1800 mg daily. In contrast, a prospective randomised placebo-controlled interventional trial on calcium carbonate 1200 mg daily showed no excess cardiovascular risk after 5 years of follow-up, nor was there any increase in death or hospitalization from atherosclerotic vascular disease after another 4.5 years of the post-trial observational study [23] (*Level Ib*). 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 [24] (*Level Ib*). These results are not directly comparable as the prospective trials examined death, hospitalization rates and overall vascular mortality, rather than MI. In the meta-analysis, cardiovascular events were not the primary endpoint in the trials included, which may have been a source of error. A recent meta-analysis of randomised controlled trials of calcium with or without vitamin D vs placebo showed no increase in the risk of coronary heart disease (which included MI, angina pectoris, acute coronary syndrome and chronic coronary heart disease) with a relative risk of 1.02 (95% CI, 0.96–1.09;  $p = 0.51$ ) [25].

Calcium-rich foods have not been associated with a higher risk of coronary heart disease [26] (*Level III*). Therefore, given the above arguments, the current recommendation is to have adequate calcium intake from food sources [27] (*Grade C, Level IV*). Optimization of vitamin D status to facilitate absorption of dietary calcium remains a sensible measure for the maintenance of bone health [28] (*Grade C, Level IV*).

We recommend that the total intake of calcium is 1,000 mg daily, both from the diet and supplements (*Grade C, Level IV*).

### 3.3.2. Vitamin D

For adults 50 years old or older, the Malaysian Recommended Nutrient Intake advocates 400 IU of vitamin D per day [20], but many experts recommend up to 800 IU per day [28] (*Grade C, Level IV*). As discussed above, it would seem that the addition of vitamin D did not reduce the elevated risk of cardiovascular events observed with calcium supplementation [22] (*Level Ia*). Blood levels of 25(OH)D provide the best index of vitamin D stores [28]. It has been suggested that levels of 25(OH)D of >20 ng/ml (50 nmol/l) are adequate for optimal skeletal health [28] (*Grade C, Level IV*). We recommend that the intake of vitamin D is 800 IU daily, to maintain levels of 25(OH)D at least above 20 ng/ml, and ideally above 30 ng/ml (75 nmol/l) [29]. However, to raise the blood level of 25(OH)D consistently above 30 ng/ml may require at least 1500–2000 IU daily of vitamin D [29] (*Grade C, Level IV*).

### 3.3.3. Bisphosphonates

Bisphosphonates are potent inhibitors of bone resorption and are effective in the treatment of OP as shown in Table 4. With increasing experience in the use of bisphosphonates, 2 adverse effects have been noted with long-term bisphosphonate therapy, i.e. atypical femoral fractures and osteonecrosis of the jaw.

### 3.4. Atypical femoral fractures

Atypical femoral fractures (AFF) have been increasingly recognised in patients on long-term bisphosphonate therapy. However, although current evidence has not definitely established a causal association between bisphosphonate use and these AFFs, the evidence for an association is quite robust [30] (*Level III*).

In a meta-analysis, the overall pooled estimate of adjusted risk ratio for AFF associated with bisphosphonates using data from the five case-control and six cohort studies was 1.70 (95% CI, 1.22–2.37). A large amount of heterogeneity was noted ( $I^2$  89.19%,  $p < 0.05$ ) [31] (*Level Ia*). Although the relative risks of AFFs are very high in patients on bisphosphonates, ranging from 2.1 to 128, their absolute risk is extremely low, ranging from 3.2 to 50 cases per 100,000 person-years [30] (*Level III*). AFFs appear to be more common in patients who have been exposed to long-term bisphosphonates, usually for more than 3 years (median treatment 7 years), but every series includes patients who have not been treated with bisphosphonates,

suggesting that the “background rate” of AFFs in OP patients is not zero [30] (*Level III*). In a study looking at Swedish women who were on bisphosphonates, the risk of AFFs declined by 70%/year (OR 0.28; 95% CI, 0.21–0.38) after the bisphosphonates were stopped [32] (*Level III*).

Nevertheless, the benefits of bisphosphonate therapy, by reducing classical osteoporotic fractures, outweigh the rare risk of AFFs [30,33] (*Level III*).

### 3.5. Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) can be diagnosed if all of the following characteristics are present -current or previous treatment with antiresorptive and/or antiangiogenic agents, exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than eight weeks, and no history of radiation therapy to the jaws or obvious metastatic disease to the jaws [34]. Classical risk factors for development of ONJ include dentoalveolar surgery, periodontal disease, trauma, poorly fitting dentures, obesity, smoking, and glucocorticoid and high-dose IV bisphosphonate therapy [35] (*Level IV*).

The frequency of ONJ in osteoporotic patients is rare, ranging from 1.04 to 69 per 100,000 patient-years in those on oral bisphosphonates to 0–90 per 100,000 patient-years for those on IV bisphosphonates [35] (*Level III*). The best current estimate for the risk of ONJ among patients exposed to oral bisphosphonates following tooth extraction is 0.5% [36] (*Level III*).

For patients receiving oral bisphosphonate therapy to manage OP, the prevalence of ONJ increases over time from near 0 at baseline to 0.21% after four or more years of bisphosphonate exposure. The median duration of bisphosphonate exposure for patients with ONJ and ONJ-like features was 4.4 years [34] (*Level III*). As a guide, for individuals who have taken an oral bisphosphonate for less than four years and have no clinical risk factors, no alteration or delay in any elective invasive dental surgery is necessary. For those who have taken more than 4 years of bisphosphonate treatment, consider discontinuation of the oral bisphosphonate (drug holiday) for at least two months prior to oral surgery, if systemic conditions permit. The anti-resorptive should not be restarted until osseous healing has occurred [34] (*Level IV*).

### 3.6. Guidelines for use of bisphosphonates

With the above in mind, it is recommended that patients who are deemed to be at low risk of osteoporosis-related fractures should not be started on bisphosphonates [30]. The efficacy of bisphosphonate therapy should be evaluated after 3–5 years [37]. 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:

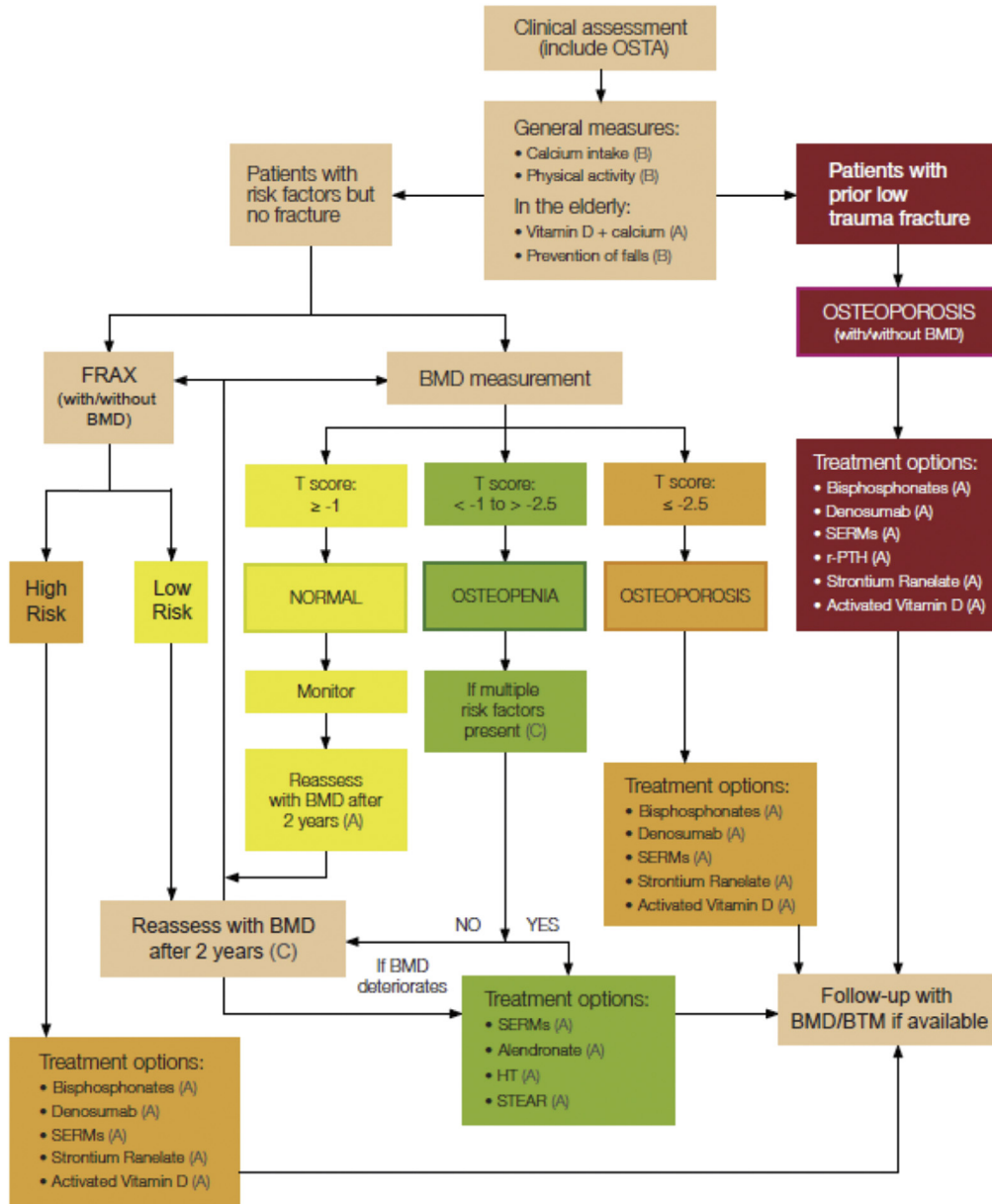


Fig. 1. Algorithm for the management of postmenopausal osteoporosis. Abbreviations for Fig. 1. BMD = Bone mineral density, BTM = Bone turnover markers, FRAX = Fracture Risk Assessment Tool, HT = Hormone therapy, OSTA = Osteoporosis Self-Assessment Tool for Asians, r-PTH = Recombinant parathyroid hormone, SERM = Selective estrogen receptor modulator, STEAR = Selective tissue estrogenic activity regulator.

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 every 2–3 years. In patients with:

- a low risk of fracture, consider a drug holiday

- evidence of AFF, bisphosphonate therapy should be discontinued
- a high risk of fracture, consider continuing bisphosphonate therapy, up to 10 years [38].

(Grade C, Level IV)

### 3.7. Algorithm for the treatment of postmenopausal OP

Following clinical assessment, all patients should be advised on general measures to improve bone health. In

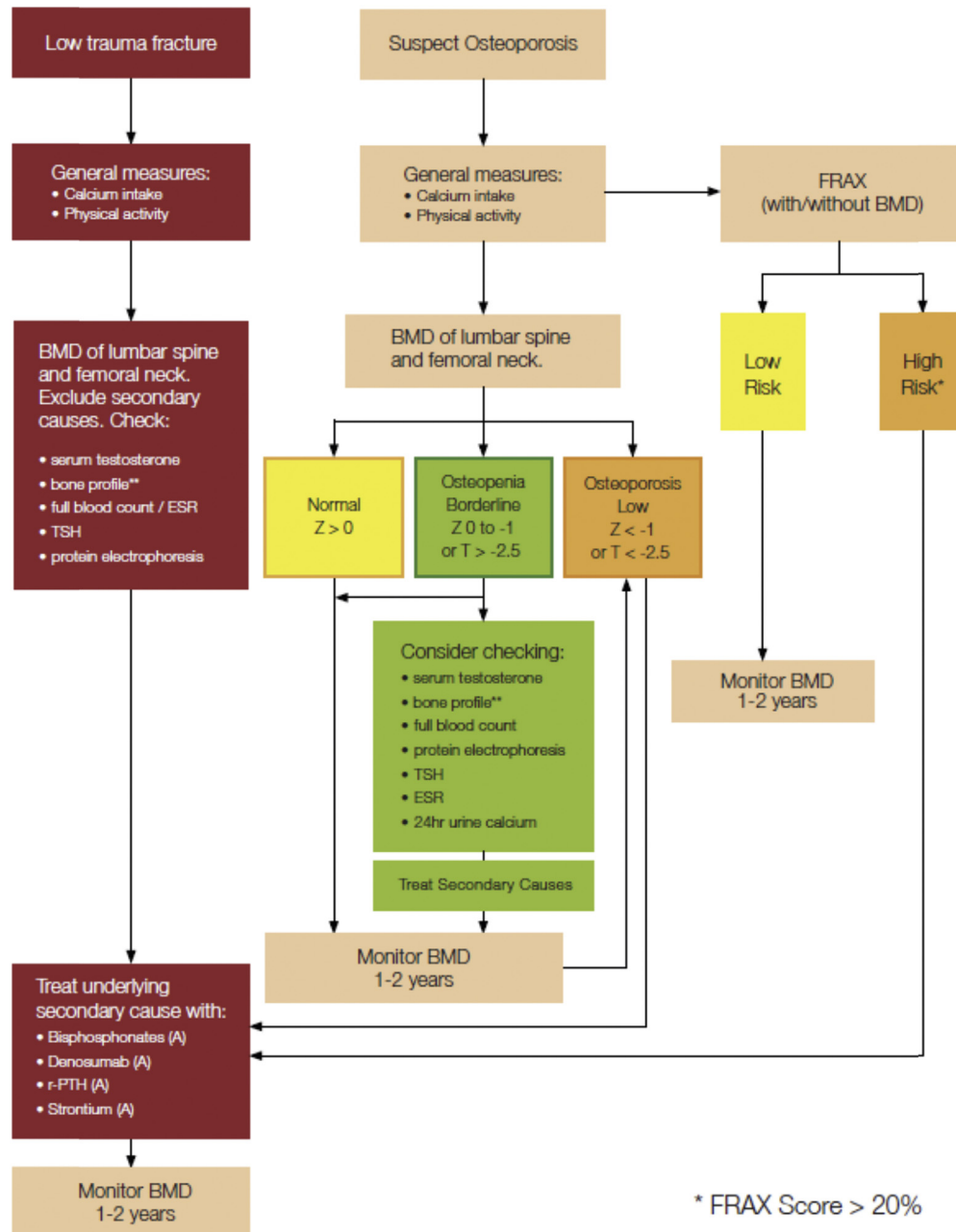


Fig. 2. Algorithm for the management of male osteoporosis. \*\*Bone Profile = Calcium, phosphate, alkaline phosphatase, albumin, creatinine, ESR = Erythrocyte Sedimentation Rate, TSH = Thyroid Stimulating Hormone.

patients who have already had a prior low trauma/fragility fracture, without any cause to suggest secondary OP, treatment can be started; measurement of BMD is ideal if available. For those with risk factors but no prior fracture, assessment using the FRAX tool is suggested. This can be used with or without a BMD measurement. In patients found to have a high 10-year risk of fracture with FRAX, treatment should be started. In patients with a low risk of fracture, BMD can be measured and monitored at 1–2 yearly intervals. If FRAX is not available, and there is still concern about the possibility of OP, a BMD measurement can be obtained. Patients with a T score  $\leq -2.5$  have OP and should be started on treatment. Patients with

osteopenia (T-score between  $-1.0$  and  $-2.5$ ) can be treated if there are multiple risk factors present, and a FRAX assessment is not available. Patients with a normal T-score ( $> -1.0$ ) can be monitored with 1–2 yearly BMD measurements. The suggested pathway for the management of postmenopausal OP is shown in Fig. 1.

#### 4. Male osteoporosis

Men account for up to 30% of hip fractures and 20% of clinical vertebral fractures [66] (Grade B, Level III). In 50% of

osteoporotic men, an underlying cause can be identified (secondary OP) [66].

Management consists of identifying and treating underlying causes. Androgen treatment is beneficial in hypogonadal men [67]. The following have been shown to increase BMD in men with OP - once weekly alendronate [68], once weekly risedronate [69], once monthly ibandronate [70], IV zoledronate [71], teriparatide (r-PTH) [72], denosumab [73] and strontium ranelate [74], but only alendronate [68] and risedronate [75] have been shown to reduce vertebral fracture (*Grade A, Level Ib*). The suggested pathway for the management of male OP is shown in Fig. 2.

The key recommendations are summarised in Appendix 3.

In conclusion, we hope that this guidance document will help health care practitioners when making clinical decisions

on managing their patients with OP. This article is not meant to be a comprehensive review of all aspects of OP, neither is it prescriptive; it is meant to be a short but practical and relevant guide through the OP literature, with final decisions made after consideration of the individuals' benefits and risks.

### Conflicts of interest

All the authors of this guidance have declared no conflicts of interest. The development of this guidance was fully funded by MOS.

## Appendix 1.

### Levels of evidence and grades of recommendation.

#### Levels 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 Guideline Clearinghouse ([www.guidelines.gov](http://www.guidelines.gov)), Agency for Healthcare Research and Quality, U.S. Department of Health & Human Services, USA [4].

#### Grades of recommendation

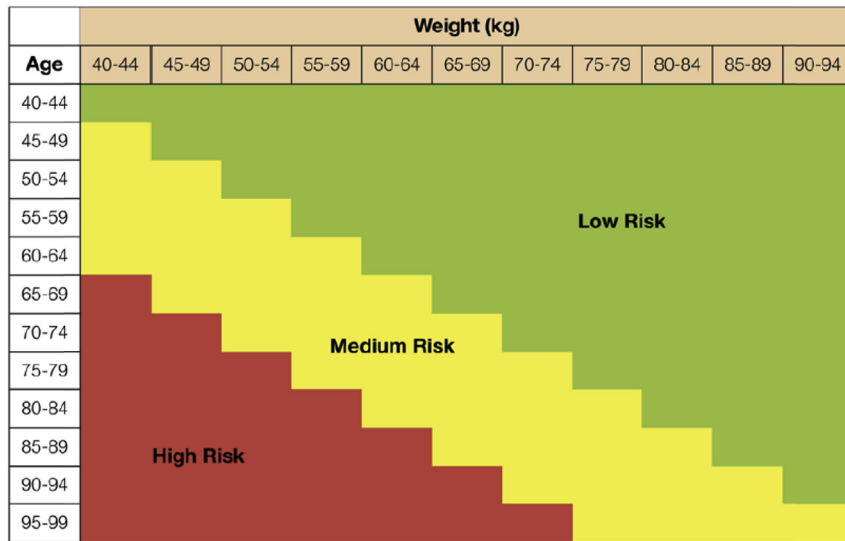
Grade	Recommendation
A (evidence levels Ia and Ib)	Requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B (evidence levels IIa, IIb and III)	Requires availability of well conducted clinical studies but no randomized 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) [5].



**Appendix 2.**

Osteoporosis Self-Assessment Tool for Asians [7]



	Implications	Recommendation
High risk	61% will have OP on BMD measurement	Suggest to measure BMD and consider pharmacologic treatment if BMD is not available, especially if other risk factors are present
Medium risk	15% will have OP on BMD measurement	Suggest measure BMD and consider pharmacologic treatment if BMD is low
Low risk	3% will have OP on BMD measurement	BMD measurement is usually not necessary unless other risk factors are present

BMD: bone mineral density, OP: osteoporosis.

**Appendix 3.**

*Key Recommendations*

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 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. The evidence for the efficacy of these preventative measures is shown in Table 3.

(Grade C, Level IV)

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

(Grade C, Level IV)

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  $\leq -2.5$ . In patients with osteopenia, initiation of treatment is recommended with a FRAX<sup>®</sup> fracture probability of more than 3% for the hip or 20% for major osteoporotic fracture at 10 years.

(Grade C, Level IV)

The evidence for the efficacy of medications available for the treatment of OP is shown in Table 4. The choice of drug for established osteoporosis, especially those with previous fracture must be an agent shown not only to increase BMD, but also proven to reduce fracture both at the spine and hip.

(Grade C, Level IV)

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

(Grade C, Level IV)

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

(Grade A, Level Ib)

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