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Review article

A summary of the Malaysian Clinical Practice Guidelines on the management of postmenopausal osteoporosis, 2022

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ABSTRACT

Objectives: The aim of these Clinical Practice Guidelines is to provide evidence-based recommendations to assist healthcare providers in the screening, diagnosis and management of patients with postmenopausal osteoporosis (OP).
Methods: A list of key clinical questions on the assessment, diagnosis and treatment of OP was formulated. A literature search using the PubMed, Medline, Cochrane Databases of Systematic Reviews, and OVID electronic databases identified all relevant articles on OP based on the key clinical questions, from 2014 onwards, to update from the 2015 edition. The articles were graded using the SIGN50 format. 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 OP. Risk stratification of patients with OP encompasses clinical risk factors, bone mineral density measurements and FRAX risk estimates. Non-pharmacological measures including adequate calcium and vitamin D, regular exercise and falls prevention are recommended. Pharmacological measures depend on patients' fracture risk status. Very high-risk individuals are recommended for treatment with an anabolic agent, if available, followed by an anti-resorptive agent. Alternatively, parenteral anti-resorptive agents can be used. High-risk individuals should be treated with anti-resorptive agents. In low-risk individuals, menopausal hormone replacement or selective estrogen receptor modulators can be used, if indicated. Patients should be assessed regularly to monitor treatment response and treatment adjusted, as appropriate.

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Conclusions: The pathways for the management of postmenopausal OP in Malaysia have been updated. Incorporation of fracture risk stratification can guide appropriate treatment.

1. Introduction

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength, making a person to be susceptible to low trauma fracture (fracture after a fall from standing height). Osteoporosis is diagnosed based on a T-score of −2.5 or lower on bone mineral density (BMD) measurement by dual-energy X-ray absorptiometry (DXA) at the femoral neck, total hip or lumbar spine (Table 1) [1]. Notably, a clinical diagnosis of osteoporosis can be made after a low trauma spine or hip fracture, irrespective of BMD measurements [1].

Hip fractures are associated with high morbidity and a mortality rate of up to 20% in the first year. Majority of those who survive are disabled and only 25% will resume normal activities [2].

The Asian Federation of Osteoporosis Societies study estimated that the number of hip fractures in Malaysia would increase from 5,880 in 2018 to 20,893 in 2050. The estimated direct medical cost of hip fractures would also increase from US$ 35.3 million in 2018 to US$ 125.4 million in 2050. This is an underestimation of the total economic burden, as it does not consider the costs incurred in rehabilitation and long-term nursing care [3].

The Malaysian Clinical Practice Guideline (CPG) for the management of osteoporosis was first published in 2001. Subsequent versions were published with the last update taking place in 2015. Since then, advances have been made in the management of osteoporosis necessitating the need to provide an updated CPG for healthcare professionals.

2. Methods

A multidisciplinary guideline development group was formed. There were 20 experts in the guideline development group representing rheumatology (2), endocrinology (7), geriatric medicine (4), orthopaedic surgery (3), family medicine (1), gynaecology (1), dietetics (1) and pharmacy (1).

The previously published 2015 Clinical Guidance for the Management of Osteoporosis was used as a baseline. A literature search was carried out at the following electronic databases: PubMed, Medline, Cochrane Databases of Systematic Reviews (CDSR), and OVID from January 2014 until March 2022. In addition, the reference lists of relevant articles were searched to identify further studies. Reference was also made to the latest edition of other guidelines on the management of osteoporosis including the guidelines developed by the American Association of Clinical Endocrinologists/American College of Endocrinology [1], Bone Health and Osteoporosis Foundation [4], European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases – International Osteoporosis Foundation [5], International Society for Clinical Densitometry [6], and the National Institute for Health and Care Excellence [7].

The scope and framework of the CPG was determined by the chairpersons. An expert panel was recruited based on their expertise in the various aspects of OP. Clinical questions were assigned to specific members of the guideline development group for literature review and formulation of the recommendations. The chairpersons reviewed individual contributions and sought clarification as required before merging all the recommendations into 1 document. A virtual consensus meeting was held with all members to review the initial draft, following which edits and amendments were made. A second virtual consensus meeting was held to approve amendments and draft out the algorithms. The final document was approved via email by the expert panel.

The articles were graded using the SIGN (Scottish Intercollegiate Guidelines Network) 50 format that includes criteria for the levels of evidence and grades of recommendations (Appendix 1) [8]. For each recommendation and statement in the text, studies with the highest levels of evidence were used to frame them.

3. Results and discussion

The key statements and recommendations are detailed in Appendix 2. The following sections discusses some of the underlying research that led to the development of the statements and recommendations.

3.1. Assessment

3.1.1. Screening and diagnosis

In individuals with prior low-trauma fractures, those with clinical risk factors, those who have conditions that can cause secondary osteoporosis, those who are at high risk of falls, and for all postmenopausal women aged ≥50 years, screening for osteoporosis is recommended [1].

A diagnosis of osteoporosis is usually made only after a low-trauma fracture as most patients tend to be asymptomatic. Common fracture sites due to osteoporosis are the hip, spine and forearm. Other clinical presentations include increasing dorsal kyphosis (Dowager's hump), historical height loss of 4 cm or more (1.5 inches or more) and acute back pain following seemingly innocuous activities (such as bending, lifting objects, coughing or sneezing) [1,7].

BMD measurement via dual-energy X-ray absorptiometry (DXA) at the femoral neck, total hip or lumbar spine is the gold standard assessment for diagnosing osteoporosis [1,6]. Among patients with hyperparathyroidism and severe obesity (beyond the weight limit for the DXA table), the hip and/or spine cannot be measured or

Table 1
Classification of osteoporosis for postmenopausal women [1].

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 > 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.

interpreted and therefore, forearm BMD (distal 1/3 radius of the non-dominant forearm) should be measured [6].

3.1.2. Risk stratification and starting treatment

An effective osteoporosis screening tool can prioritize patients at high risk of osteoporosis and stratify the need for DXA scans. Country-specific fracture risk assessment should be used to assess bone health and predict future fracture risk [9]. In Malaysia, we can use Osteoporosis Self-Assessment Tool for Asians (OSTA) [10], and Malaysian Osteoporosis Screening Tool (MOST) [11] as screening tools, whilst FRAX® can be used as a fracture risk assessment tool [12].

Among untreated patients aged 40–90 years, FRAX® estimates the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus or forearm). Clinical risk factors included in FRAX® are age, sex, weight, height, prior fracture, parental history of hip fracture, smoking, long-term use of glucocorticoids, rheumatoid arthritis and alcohol consumption [12]. Although BMD is not mandatory for calculating FRAX® estimates, its inclusion can improve the prediction of fracture probability.

To date, there is no Malaysia-specific FRAX® tool. Therefore, this guideline recommends the use of other ethnic specific algorithms such as Singapore Chinese, Hong Kong Chinese, Singapore Malay and Singapore Indian, until local data is available in Malaysia.

The treatment interventions in FRAX® are partly based on cost-effectiveness, for which there is no Malaysian data. Nevertheless, among patients with osteopenia, treatment initiation is recommended with a FRAX® (or if available, trabecular bone score [TBS]-adjusted FRAX®) estimate of > 3% probability at 10 years for hip or > 20% probability at 10 years for major osteoporosis-related fracture [1]. Adjustments to the FRAX® estimates are required for specific populations such as those with long-term use of glucocorticoids and type 2 diabetes [1].

3.2. Non-pharmacological treatment

3.2.1. Calcium and vitamin D

Adequate calcium and vitamin D is important for peak bone mass attainment to prevent osteoporosis in later life [13]. Increasing calcium intake from dietary sources or by taking calcium supplements produces small non-progressive increases in BMD by 0.7%–1.8% at 2 years, an increase that is unlikely to be clinically significant in reducing risk of fractures [14]. Subsequent meta-analyses further reported that calcium supplementation on its own would not lower the risk of vertebral or hip fractures [15–17]. This CPG recommends an intake of 1200 mg/day of calcium. It is important to consider the different percentages of elemental calcium and ranges of calcium absorption from different formulations.

Vitamin D supplements are available as either ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3). Vitamin D2 is derived from plant sources and vitamin D3 from animal sources or exposure to sunlight [18]. Blood levels of 25-hydroxy vitamin D (25(OH) D) provide the best index of vitamin D stores. Different threshold levels have been put forth as optimal for skeletal health. This CPG recommends a 25(OH)D level above 30 ng/ml (75 nmol/L). This level could reduce falls among older people, which could indirectly reduce the risk of fractures [19]. For adults who are vitamin D deficient, the CPG recommends treatment with 50,000 IU of vitamin D2 or vitamin D3 once a week for 8 weeks or its equivalent of 6000 IU of vitamin D2 or vitamin D3 daily followed by maintenance therapy of 800–1000 IU/day.

Routinely, both calcium and vitamin D are prescribed together. A meta-analysis showed that calcium and vitamin D supplementation on its own led to a modest reduction in fracture risk especially those at highest risk of calcium and/or vitamin D deficiency [20]. Additionally, calcium plus vitamin D supplementation significantly reduced the risk of total fractures by 15% (summary relative risk estimate [SRRE] 0.85, 95% Confidence Interval [CI] 0.73, 0.98) and hip fractures by 30% (SRRE 0.70, 95% CI 0.56, 0.87) among older people [13]. There is inadequate evidence that calcium with or without vitamin D supplementation increases cardiovascular risk [21]. Both calcium and vitamin D are prescribed alongside pharmacological treatments of osteoporosis. This ensures both are replete while on treatment and mirrors the use of these agents in clinical trials.

3.2.2. Exercise

Regular exercise, in particular weight-bearing exercise (eg, brisk walking and line dancing) is encouraged in all age groups to maximise peak bone mass, decrease age-related bone loss, maintain muscle strength and balance [22–24].

Exercise has been shown to prevent falls and injuries from falls. A systematic review that included 116 studies involving 25,160 participants found that exercise reduces the rate of falls by 23% (pooled rate ratio 0.77, 95% CI 0.71, 0.83) compared to controls [25]. Multiple exercise component interventions (i.e. combining ≥ 2 categories of exercise) have also shown to reduce rate of falls related injuries [26–29]. For exercise to be effective, it must be of sufficient intensity and duration [29]. Interventions with a total weekly dose of > 3 hrs [25,30] that included balance, functional and resistance exercises were particularly effective in reducing the rate of falls [30,31]. Exercise has also been shown to reduce the likelihood of sustaining a fracture by 26–46% [28,31,32]. These studies included either elements of resistance or strength training, gait and balance exercise, and weight-bearing component.

Current evidence is unable to make recommendation of one form of exercise over another to reduce the risk of falls and fractures. However, the evidence does support exercise to be an essential part of a person's management to reduce their risk of falls and falls-related fractures. It is also important to emphasise that exercise has to be tailored to the person's ability and health status.

3.2.3. Falls prevention

All older persons (≥ 65 years old) and adults that have sustained a fragility fracture should be screened for falls, frequency of falling, their risk of falls, gait and balance difficulties [33,34]. Those identified to be at risk should receive a multifactorial falls risk assessment and intervention.

This assessment includes gathering a detailed and focused history of fall incidents, medication review, addressing any acute or chronic medical illness, identifying any sensory (especially vision and hearing) impairment, ability to ambulate, perform activities of daily living, and an examination of gait, balance, neurological and cardiovascular system. This would usually identify multiple causes of falls which would necessitate a multifactorial individualised intervention plan for the individual (Table 2) [31,35–37].

3.3. Pharmacological treatment

In Malaysia, postmenopausal women should be considered for treatment, if they fulfil any of following, after exclusion of secondary causes of osteoporosis:

- Identification of low trauma hip, vertebral, wrist or any other major fragility fracture (clinical or asymptomatic)
- T-score ≤-2.5 at the femoral neck, total hip or lumbar spine on DXA
- In patients with osteopenia (T-score between −1.0 and −2.5) with Fracture Risk Assessment Tool (FRAX®) calculated 10-year

Table 2
Assessment of falls risk factors and intervention to reduce identified risk factors.

Assessment	Intervention
Evaluate lower limb muscle strength, gait and balance	Poor gait, strength and balance - Refer for physical therapy - Engagement in exercise programmes that involve balance, functional exercise and resistance training
Identify medications that increase fall risk	Medication(s) likely to increase fall risk - Optimise medications by stopping, switching or reducing dosage (especially for psychoactive medications)
Ask about potential home hazards	Home hazards likely to increase fall risk - Refer to occupational therapist to evaluate home safety assessment and/or modification
Measure positional blood pressure	Orthostatic hypotension observed - Review medication - Encourage adequate hydration - Consider use of compression stockings, abdominal binders or physical manoeuvres
Check visual acuity	Visual impairment observed - Refer ophthalmologist/optometrist - Avoid wearing multifocal glasses when walking particularly stairs
Assess feet and footwear	Feet or footwear issues identified - Appropriate treatment for foot problems identified - Advise wearing well fitted shoes indoors and outdoors
Assess vitamin D intake	Vitamin D deficiency observed or likely - Recommend daily vitamin D supplement for individuals with proven deficiency
Previous history of falls OR fear of falling	Provide falls education and information to all patients - Regular follow up to ensure adherence to interventions

fracture probability of > 3% for hip and > 20% for major osteoporotic related fracture

Following the decision to start pharmacological treatment, there should be a risk stratification of patients to low-risk, high-risk, and very high-risk for fractures [38]. These recommendations were made following clinical trials demonstrating the efficacy of anabolic therapies in reducing the fracture risks quickly in very high-risk individuals.

Various definitions have been proposed to stratify fracture risks for people with osteoporosis [1,38]. Until further local data is available, the CPG Working Group has decided to adopt the American Association of Clinical Endocrinologists (AACE) proposed features to identify people with very high risk of fracture [1]:

- Recent fracture (within the past 12 months)
- Fractures while on approved osteoporosis therapy
- Multiple fractures
- Fractures while on drugs causing skeletal harm (e.g. glucocorticoids)
- Previous history of injurious falls or high risk of falls
- Advanced age
- Frailty
- Very low BMD measurement (T-score <-3.0)
- Very high FRAX® risk (> 30% for major osteoporotic fracture and > 4.5% for hip fracture), or other validated fracture risk algorithms

Patients with any of the above features would be classified as in the “very high risk” group, and those without these features would be in the “high risk” or “low risk” group. Pharmacological treatment options would be based on their risk as follows (Fig. 1):

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

All pharmacological medication licensed for osteoporosis will increase BMD and reduce vertebral fractures. However, not all have been shown to reduce hip fractures. The evidence for each agent is shown in Table 3. Since the last edition of the CPG, strontium ranelate is no longer available locally. In addition, there has been more data on the long-term usage of denosumab and a new anabolic agent, romosozumab, has been licensed for use in Malaysia.

3.3.1. *Menopausal hormone therapy (MHT)*

MHT can be offered to symptomatic women under the age of 60 and within 10 years of the menopause. It is an effective treatment for moderate to severe vasomotor symptoms and genitourinary symptoms of the menopause. In addition to these symptomatic benefits, MHT will increase BMD and reduce fragility fractures [48].

However, initiation of MHT in women more than 60 years old or after 10 years of menopause for the prevention of osteoporosis fractures is not recommended [57].

A full gynaecological assessment is mandatory prior to starting MHT with the dose and type of MHT tailor-made for that individual [58].

3.3.2. *Tibolone*

Tibolone is a synthetic hormone with estrogenic, progestogenic, and androgenic properties. It is used for relief of menopausal symptoms and for the prevention of OP in postmenopausal women [55,59].

3.3.3. *Raloxifene*

Raloxifene is a selective estrogen receptor modulator (SERM)

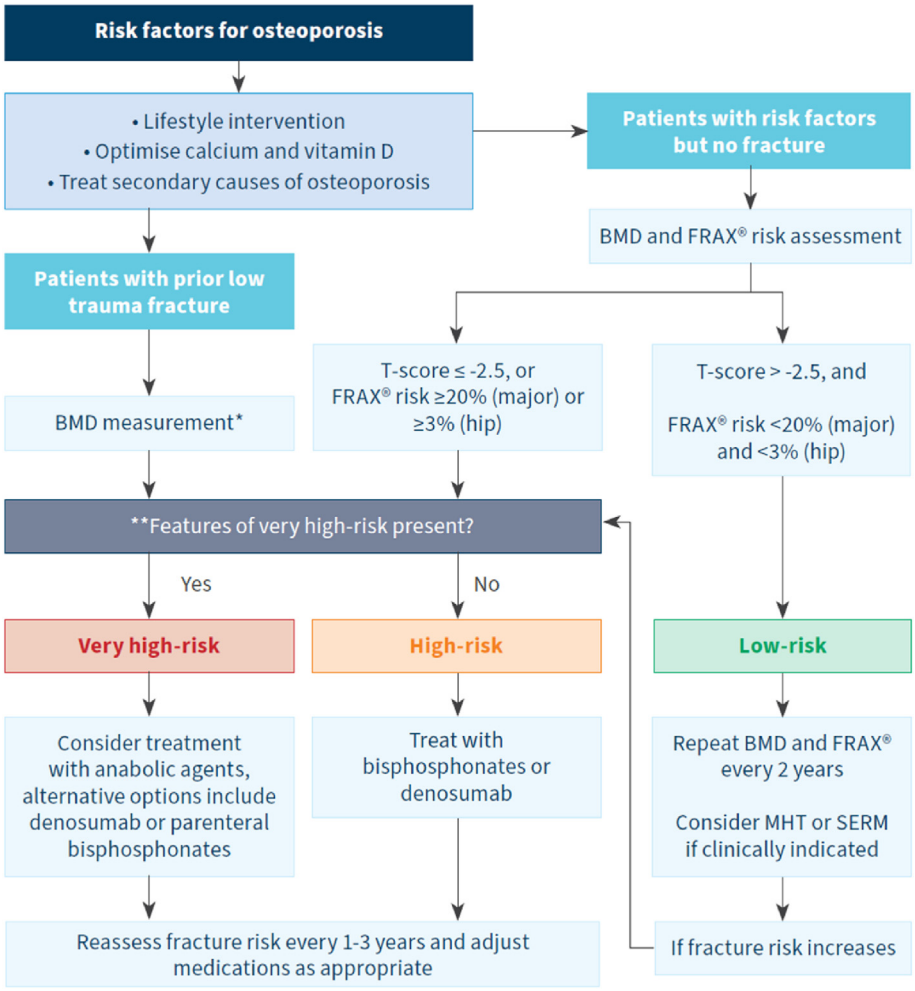

Fig. 1. Treatment sequence in postmenopausal osteoporosis
*BMD measurement is not necessary for treatment initiation, but will be useful for monitoring treatment.
**Refer to features of very high-risk in section 3.3.
BMD, bone mineral densitometry; FRAX®, Fracture Risk Assessment Tool; MHT, menopausal hormone therapy; SERMs, selective estrogen receptor modulators.

Table 3
The strength of recommendations concerning interventions in the treatment of osteoporosis Note: The grade of recommendation shown in this table relates to the strength of the evidence on which the recommendation is based as defined by SIGN (see Appendix 1). It does not reflect the clinical importance of the recommendation.

Intervention	BMD Improvement	Decrease Vertebral Fracture Rate	Decrease Hip Fracture Rate
Alendronate [39–41]	A	A	A
Calcitriol/Alfacalcidol [42,43]	A	A	A
Calcium [16,17]	A	A	–
Calcium + vitamin D [16,44]	A	–	A
Denosumab [45]	A	A	A
Ibandronate [46,47]	A	A	–
Menopausal Hormone Therapy [48]	A	A	A
Raloxifene [49]	A	A	–
Risedronate [50,51]	A	A	A
Romosozumab [52]	A	A	–
r-PTH/teriparatide [53,54]	A	A	–
Tibolone [55]	A	[a]	–
Zoledronate [56]	A	A	A

BMD, bone mineral density.
[a] Effect seen in post-hoc analysis in selected groups of patients.

that bind to estrogen receptors throughout the body. It has been shown to increase BMD and reduce vertebral fractures in post-menopausal women [49]. In addition, patients with OP on raloxifene had a reduction in the risk of estrogen receptor-positive invasive breast cancer compared to those on placebo [60].

3.3.4. Bisphosphonates

Bisphosphonates are potent inhibitors of bone resorption and are effective treatments for OP. They can be given orally at weekly (alendronate, risedronate) or monthly (ibandronate) intervals, or once a year intravenously (zoledronate) [39–41,46,47,50,51,56]. As shown in Table 3, all bisphosphonates increase BMD and reduce vertebral fractures. Alendronate, risedronate and zoledronate also reduce hip fracture rates [39–41,50,51,56].

The long-term use of bisphosphonates has been complicated by the risk of atypical femoral fractures (AFF) and osteonecrosis of the jaw (ONJ) during treatment. For AFF, the age-adjusted incidence rate has been estimated to be 1.78 per 100,000 person-years in patients on bisphosphonate use < 2 years and the incident rate increases to 113.1 per 100,000 person-years with > 8 years' duration [61]. It has been shown that Asians on bisphosphonate therapy may have an increased risk of AFF compared to Caucasians [62]. Patients on anti-resorptive therapy who develop thigh pain should have imaging performed to look for evidence of stress changes in the femur within the AFF spectrum [63]. Overall, the benefit of reducing further osteoporotic fractures with bisphosphonate treatment is much greater than the small absolute risk of AFFs [62,64,65].

The management of AFF depends on whether it is incomplete or complete [64]. All patients should discontinue their anti-resorptive treatment and maintain an adequate calcium and vitamin D intake. For those with an incomplete AFF without pain, a trial of conservative management for 2–3 months is proposed. However, if there is no radiographic improvement or it becomes symptomatic, prophylactic nail fixation is strongly recommended because these patients may progress to a complete fracture. Surgical management with intramedullary nail fixation is recommended for incomplete AFF with pain, and complete AFF. Following surgical management of AFF, further medical treatment has to balance the risk of causing new atypical fractures against the risk of fragility fractures when not treating OP. All patients with AFF should have their contralateral hip assessed for possible asymptomatic AFF.

The absolute risk of ONJ is very low ranging from 1 in 10,000 to 1 in 100,000 [66]. However, the risk of ONJ reaches 21 in 10,000 (0.21%) in patients on > 4 years of oral bisphosphonates [67]. ONJ is likely to occur earlier in those treated with intravenous versus oral forms of bisphosphonates [68] and is more commonly seen in those on oncological doses of bisphosphonates and denosumab [69]. There are no recommendations to stopping bisphosphonates for dental procedures but initiation should be deferred until the area has healed [70].

When considering the risk-benefit ratio of osteoporosis treatment with bisphosphonates, a study comparing the number of fractures in a sub-group of Asian women on bisphosphonates after 3 years of treatment reported 8 AFFs, with 91 hip fractures prevented and 330 clinical fractures prevented per 10,000 women. The benefit continued in those on bisphosphonates for up to 5 years, with 38 AFF, 174 hip fractures prevented and 524 clinical fractures prevented per 10,000 women [62]. Thus, the benefit of treatment with bisphosphonates in preventing osteoporotic fractures outweigh the small risk of side effects.

However, because of the increasing incidence of AFF and ONJ with increasing duration of bisphosphonate treatment, it is recommended that after 5 years of oral bisphosphonates or 3 years of intravenous bisphosphonates, there should be a reassessment of the patient's fracture risk [71]. The recommended duration of treatment as based on risk stratification is shown in Table 4. However, it has been shown that there is an increased risk of hip and vertebral fractures after a 2-year drug holiday for those on the oral bisphosphonates, alendronate and risedronate [72], which would suggest that patients should be reviewed no longer than 2 years after starting a drug holiday.

3.3.5. Denosumab

Denosumab is a human monoclonal antibody (IgG) that inhibits the formation, function, and survival of osteoclasts by inhibiting RANK (receptor activator of nuclear factor kappa-B) ligand, thus reducing bone resorption [73]. As shown in Table 3 and it increases BMD and reduces vertebral and hip fracture rates.

Although a potent anti-resorptive, discontinuation of denosumab is associated with a rapid rebound increase in bone turnover, loss of BMD and possible increased risk of multiple vertebral fractures especially in the high-risk group [74]. Missing or delaying denosumab doses by a few months may result in an elevated risk of vertebral fractures and should be avoided [75]. Hence the concept of a drug holiday is not applicable to denosumab. Those who have stopped denosumab should be transitioned to other treatments for osteoporosis to reduce the rebound increase in bone turnover and fracture risk associated with denosumab withdrawal [76].

3.3.6. Teriparatide

Recombinant human PTH 1–34 (r-PTH/teriparatide), is a potent anabolic agent. Teriparatide is indicated for individuals at very high risk for fractures (e.g. those with multiple vertebral fractures) or osteoporosis not responsive to other anti-osteoporosis therapy [77,78].

Current recommendation for the treatment duration of r-PTH is up to 24 months. The benefits of anabolic therapy wear off within 1 year of discontinuation [79]. Hence, the recommendation is to initiate anti-resorptive therapies when stopping anabolic therapy to maintain bone density gains [80,81].

3.3.7. Romosozumab

Romosozumab is an anabolic agent. It is a humanised monoclonal antibody that binds to sclerostin [82]. Romosozumab has been shown to increase BMD and reduce vertebral fractures (see Table 3) and is used to treat osteoporosis, especially in patients with a very high fracture risk. The recommended duration of treatment is for 12 months. Once romosozumab is stopped, BMD rapidly reduces back to baseline levels [83]. It is therefore recommended that anti-resorptive therapy is started as soon as romosozumab is stopped [82].

With regards to adverse events, the 3 major randomised Phase III trials with romosozumab [52,84,85] showed that 1.3% (N = 77) in the romosozumab arm and 0.9% (N = 53) in the control arm experienced a major adverse cardiac events (MACE) (cardiac ischaemic events and cerebrovascular events) (Hazard Ratio [HR], 1.40; 95% CI, 0.99 to 1.99) [86]. In Malaysia, romosozumab is contraindicated in patients who have had a myocardial infarction or stroke within the past 1 year.

3.4. Treatment failure

Osteoporosis treatment reduces fracture risk by 40–70% but does not eliminate the risk entirely. Patients who are on pharmacological therapy may still develop fractures and this may reflect 'residual disease'. However, do consider that there has been treatment failure when the following occurs [87]:

Table 4
Recommended duration of bisphosphonate therapy for women [71,72].

Risk Stratification	Recommended Duration of Treatment
Women at high-risk, eg, • Fracture during treatment • Low hip T-score ≤ 2.5 • High fracture risk score with FRAX® • Previous major osteoporotic fracture • Older women > 70 years old with any of the above risk factors	Continue for up to 10 years (oral) or 6 years (intravenous) with periodic evaluation
Women not at high-risk	After 3–5 years of bisphosphonate therapy, a drug holiday of 2 years can be considered

FRAX®, Fracture Risk Assessment Tool.

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

Before concluding that a treatment has failed, the following factors should be addressed:

- Duration of treatment – if the fracture occurs within the first year, before significant gain in BMD, therapy may not need to be changed [88].
- Adherence to therapy – poor adherence is common and associated with increased fracture rate of 30% at any skeletal site [89].
- Assess if there are existing secondary causes of osteoporosis or inter-current conditions which increases bone resorption [90].
- Vitamin D level – low vitamin D levels can accelerate bone loss and reduce the efficacy of osteoporosis treatments [91,92].

4. Conclusions

We have updated the screening, diagnostic and treatment pathways for the management of osteoporosis in Malaysia to reflect current best practice. Non-pharmacological measures including adequate calcium and vitamin D, regular exercise and falls prevention are recommended. A major change is the incorporation of fracture risk stratification into very high-risk, high-risk and low-risk individuals to guide appropriate pharmacological treatment options. It is important that pharmacological treatment is started in all patients with confirmed osteoporosis.

Conflicts of interest

The authors declare no competing interests.

Acknowledgments

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Appendix 1

SIGN 50 Levels of Evidence and Grades of Recommendations

Levels of Evidence

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

Grades of Recommendation

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

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

RCT = Randomised controlled trial.

Appendix 2. Key Statements and Recommendations

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

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

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

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

BMD measurement with DXA remains the gold standard for the diagnosis of osteoporosis. [GRADE D ☑]

The use of quantitative ultrasound (QUS) in the diagnosis and monitoring of treatment in osteoporosis is not recommended. [GRADE D ☑]

Bone turnover markers (BTM) are useful for clinical monitoring of treatment response and assessment of adherence to treatment. [GRADE D ☑]

All patients commenced on active anti-osteoporosis therapy should be assessed for response to treatment. [GRADE D ☑]

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

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

Exercise and physical therapy are recommended to prevent falls and injuries from falls. [GRADE A]

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

Those at risk of falls should receive a multifactorial falls risk assessment and intervention. [GRADE A]

Hip protectors used in care home residents can reduce the risk of hip fractures. [GRADE B]

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

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

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

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

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

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

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

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

Oral bisphosphonates are not recommended for patients with an eGFR <30 ml/min (chronic kidney disease stage 4–5). [GRADE D ☑]

Zoledronic acid is contraindicated in patients with eGFR <35 ml/min. [GRADE A]

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

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

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

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

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

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

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

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

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

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

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

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