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Review article

Summary of the Thai Osteoporosis Foundation (TOPF) Clinical Practice Guideline on the diagnosis and management of osteoporosis 2021

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ABSTRACT

Objectives: The Thai Osteoporosis Foundation (TOPF) is an academic organization that consists of a multidisciplinary group of healthcare professionals managing osteoporosis. The first clinical practice guideline for diagnosing and managing osteoporosis in Thailand was published by the TOPF in 2010, then updated in 2016 and 2021. This paper presents important updates of the guideline for the diagnosis and management of osteoporosis in Thailand.

Methods: A panel of experts in the field of osteoporosis was recruited by the TOPF to review and update the TOPF position statement from 2016. Evidence was searched using the MEDLINE database through PubMed. Primary writers submitted their first drafts, which were reviewed, discussed, and integrated into the final document. Recommendations are based on reviews of the clinical evidence and experts' opinions. The recommendations are classified using the Grading of Recommendations, Assessment, Development, and Evaluation classification system.

Results: The updated guideline comprises 90 recommendations divided into 12 main topics. This paper summarizes the recommendations focused on 4 main topics: the diagnosis and evaluation of osteoporosis, fracture risk assessment and indications for bone mineral density measurement, fracture risk categorization, management according to fracture risk, and pharmacological management of osteoporosis.

Conclusions: This updated clinical practice guideline is a practical tool to assist healthcare professionals in diagnosing, evaluating, and managing osteoporosis in Thailand.

1. Introduction

The Thai Osteoporosis Foundation (TOPF) is an academic organization comprising a multidisciplinary group of healthcare professionals managing osteoporosis. The TOPF published the first clinical practice guideline for diagnosing and managing osteoporosis in Thailand in 2010, then updated in 2016 and 2021.

The TOPF Clinical Practice Guideline for the Diagnosis and Management of Osteoporosis 2021 is a systemically developed statement to assist healthcare professionals in decision-making for diagnosing and managing osteoporosis in Thailand. The guideline's scope is for postmenopausal women and men aged 50 years and older. Most of the content is based on literature reviews. In areas of uncertainty, professional judgement was applied. We encourage medical professionals to use these recommendations with their clinical judgment based on local resources and individual patient circumstances.

This guideline has been endorsed by the Royal College of Physicians of Thailand (RCPT), the Royal College of Orthopedic Surgeons of Thailand (RCOST), the Royal Thai College of Obstetricians and Gynecologists (RTCOG), the Royal College of Physiatrists of Thailand, the Royal College of Radiologists of Thailand (RCRT), the Royal College of Dental Surgeons of Thailand, the Endocrine Society of Thailand, the Thai Menopause Society, the Thai Society of Gerontology and Geriatric Medicine, the Thai Rheumatism Association, and the Thai Association of Oral and Maxillofacial Surgery under the Royal Patronage of H.M. the King.

2. Guideline development process

The TOPF enlisted a panel of 34 experts in the field of osteoporosis to review and update the 2016 TOPF position statement [1]. Evidence was searched using the MEDLINE database through PubMed. Primary writers submitted their first drafts, which were reviewed, discussed, modified, and integrated into the final document. Recommendations are based on reviews of the clinical evidence and experts' opinions. They are classified using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) System. The recommendations' grading and the evidence's qualities are shown in Tables 1 and 2. The target users are all healthcare professionals involved in osteoporosis care in Thailand.

3. Summary of main recommendations

The current guideline consists of 90 recommendations divided into 12 main topics. This paper summarizes the recommendations focused on 4 main topics that may differ among countries: the diagnosis and evaluation of osteoporosis, fracture risk assessment and indications for bone mineral density (BMD) measurement, fracture risk categorization and management according to fracture risk, and pharmacological management of osteoporosis.

The topics that are not included are as follows: non-pharmacological management, treatment monitoring, a fragility fracture during osteoporosis treatment, management of patients who are unable to receive ongoing injectable osteoporosis drugs due to COVID-19, atypical femoral fracture, osteonecrosis of the jaw, and multidisciplinary care of osteoporosis and osteoporotic fractures. These topics are not included because they are likely the same as those in the international guidelines due to limited local studies.

4. Diagnosis and evaluation of osteoporosis

Osteoporosis can be diagnosed based on the criteria shown in Table 3. Fragility hip fracture is a common and severe complication of osteoporosis leading to disability, mortality [2–6], and high healthcare costs [7]. Fragility vertebral fracture is also common [8,9]. Although most patients are asymptomatic, they have an increased risk of recurrent vertebral and nonvertebral fractures,

Table 1
Grading of recommendations.

I	Strongly recommended
IIa	Conditionally recommended
IIb	Neither recommended nor against
III	Not recommended

Table 2
Quality of evidence.

	Quality of evidence	Study designs
A	**High**	Meta-analyses of randomized controlled trials Randomized controlled trials (≥2 trials)
B	**Moderate**	One randomized controlled trial Meta-analyses of non-randomized controlled trials Large, well-designed, non-randomized controlled trials
C	**Low**	Other study designs such as descriptive studies, retrospective studies
D	**Very low**	No evidence (experts' opinions)

Table 3
Diagnosis of osteoporosis.

Diagnostic criteria (One of the following criteria)		Grading of recommendations	Quality of evidence
1	A fragility vertebral or hip fracture	I	B
2	T-score ≤ −2.5[a]	I	B
3	T-score between −1.0 and −2.5 and a 10-year probability of hip fracture ≥ 3%[b]	IIa	B
4	T-score between −1.0 and −2.5 and a fragility fracture of the proximal humerus, pelvis, or distal forearm	IIa	C

[a] T-score at the L-spine, femoral neck, total hip, or distal 1/3 radius (L-spine and hip are the preferred sites for BMD measurement).
[b] FRAX for Thai.

including hip fractures [10–14]. BMD T-scores less than or equal to −2.5 is associated with increased fracture risk [15–21]. However, most patients presenting with fragility fractures had T-scores between −1.0 and −2.5 [22–25]. Therefore, they should be diagnosed with osteoporosis if they have a BMD T-score in osteopenic ranges with a 10-year probability of hip fracture assessed by Thai FRAX 3% or more or with a fragility fracture of the proximal humerus, pelvis, or forearm [18–20,26]. Due to limited data on the major osteoporotic fractures in the Thai populations, our diagnostic criteria did not include a 10-year probability of major osteoporosis fracture.

A detailed history, physical examination, and laboratory evaluation should be performed to exclude other metabolic bone disorders (eg, primary hyperparathyroidism, malignancy, osteomalacia, Paget's disease of bone, and chronic kidney disease-mineral and bone disorder). The recommended initial laboratory testings are blood tests for complete blood count, calcium, phosphate, electrolytes, creatinine, liver function tests, 25-hydroxyvitamin D, and 24-h urine calcium. Additional investigations are required if indicated. Secondary causes of osteoporosis, including chronic medical conditions or medications associated with bone loss or increased risk of fracture, should be evaluated and treated. The secondary causes of osteoporosis are shown in Table 4. Assessment for asymptomatic vertebral fractures is recommended in patients with the indications shown in Table 5. The assessment methods are vertebral fracture assessment by the DXA scan or lateral thoracolumbar spine X-ray.

5. Fracture risk assessment and indications for BMD measurement

Evaluation of fracture risk should be performed in individuals with clinical risk factors of osteoporosis, including postmenopausal women and men aged 50 years or older, presenting with a fragility fracture, having a disease or condition, or taking medication associated with bone loss or increased fracture risk [1,18,27]. The assessment methods include a detailed history and physical examination, FRAX without femoral neck bone mineral density (BMD), and BMD measurement by dual energy X-ray absorptiometry (DXA) scan when indicated. The indications for BMD measurement by DXA scan are shown in Table 6.

6. Fracture risk categorization and management according to fracture risk

The fracture risk can be categorized into 4 groups based on previous fragility fracture(s), T-scores, a 10-year probability of hip fracture assessed by FRAX for Thai, and clinical risk factors. The details are shown in Table 7.

Criteria for very high fracture risk were developed after an extensive discussion on the Thai health economic viewpoint. Risks of second hip fractures are highest during the first 12 months after the first fracture [28–36], especially in patients age 65 years or older with a BMD T-score of −2.5 or lower [15,21–26]. Risks of vertebral fractures are very high in patients with previous vertebral fractures [32,36], particularly incident fractures [13] with moderate to severe deformity [37]. Patients with multiple fractures, including bilateral hip fractures, hip and vertebral fractures, and fractures 3 times or 3 sites, should be categorized as very high fracture risk. Osteoporosis drugs substantially decrease fracture risk; therefore, if patients sustained a fragility fracture despite receiving osteoporosis drugs for at least 2 years without any evidence of secondary osteoporosis, their future fracture risk is very high [18]. Very low BMD T-scores in women age 65 or older and men age 70 or older should also be a very high fracture risk [15,21].

Due to limited data on the major osteoporotic fractures in the Thai database for the FRAX calculation, the major osteoporotic fracture risk was not included in the criteria for fracture risk categorization.

The management recommendations according to fracture risk are shown in Table 8.

The optimal management of patients at very high risk is sequential therapy with an osteoanabolic drug followed by an antiresorptive drug. Evidence from randomized controlled studies showed superiority in reducing fracture risks and increasing BMD over antiresorptive monotherapy [38,39]. Injectable antiresorptive drugs and oral bisphosphonates may be considered alternatives.

The appropriate treatment for patients at high fracture risk is antiresorptive drugs. Several randomized controlled studies showed benefits in reducing fracture risks and increasing BMD [40–56]. Bisphosphonates are recommended as the initial therapy. Evidence from randomized controlled studies showed broad-spectrum anti-fracture efficacy [40–43,53,54,56]. In addition, the availability of generic bisphosphonates increases the cost-

Table 4
Secondary causes of osteoporosis.

Endocrine disorders	Acromegaly
	Diabetes mellitus (type 1 and type 2)
	Growth hormone deficiency
	Hypercortisolism
	Hyperparathyroidism
	Hyperthyroidism
	Hypogonadism
Rheumatological disorders	Rheumatoid arthritis
	Ankylosing spondylitis
	Systemic lupus erythematosus
Haematological disorders	Multiple myeloma
	Monoclonal gammopathy of undetermined significance
	Beta thalassemia major
	Systemic mastocytosis
Gastrointestinal disorders	Chronic liver disease
	Inflammatory bowel disease
	Primary biliary cirrhosis
	Malabsorption syndrome
	Post gastric bypass surgery
Neurological disorders	Epilepsy
	Parkinsonism
	Stroke
Nephrological disorders	Idiopathic hypercalciuria
	Chronic kidney disease
	Renal tubular acidosis
Other medical conditions	Acquired immunodeficiency syndrome
	Chronic obstructive pulmonary disease
	Post-transplantation
	Malnutrition
Genetic disorders	Osteogenesis imperfecta
	Marfan's syndrome
	Ehlers-Danlos syndrome
Medications	Anti-epileptic drugs
	Aromatase inhibitors
	Anticoagulant (heparin, warfarin)
	Immunosuppressant (cyclosporine A, tacrolimus)
	Glucocorticoids
	Gonadotropin-releasing hormone agonist
	Medroxyprogesterone acetate
	Pioglitazone
	Proton pump inhibitor
	Selective serotonin-reuptake inhibitor

Table 5
Indications for screening vertebral fractures.

T-score < −1.0 with one of the following criteria
- Women age ≥ 70 years or men age ≥ 80 years
- Height loss (≥ 4 cm without record or ≥ 2 cm with a record)
- A history of the vertebral fracture without a medical record
- Long-term glucocorticoid therapy (prednisolone ≥ 5 mg/day or equivalent for ≥ 3 months)
T-score ≤ −2.5
A fragility fracture

effectiveness of therapy. Other alternatives are denosumab, raloxifene, and menopausal hormone therapy. In some conditions where antiresorptive drugs cannot be used, treatment with calcium and vitamin D supplements, lifestyle modification, and fall prevention are recommended.

Choices of osteoporosis drugs should be individualized based on efficacy, safety, co-morbidities, fracture risk, and patients' preferences. Osteoporosis drugs are not recommended for patients at low to moderate fracture risk. Lifestyle modification and fall prevention strategies are recommended for all patients.

Lifestyle modifications include regular weight-bearing and resistance exercises, quitting smoking, and limited alcoholic drinking (not exceeding 1 unit/d for women and 2 units/d for men). Multifactorial fall risk assessment and multicomponent intervention for fall prevention are recommended.

Table 6
Indications for bone mineral density measurement by DXA scan.

Women ≥ 65 years and men ≥ 70 years
Early menopause (before 45 years), including surgical menopause
A history of hypoestrogenism ≥ 1 year before menopause, excluding pregnancy and lactation
- Receiving GnRH agonist
- Functional hypothalamic amenorrhea, eg, medical condition, excessive exercise, anorexia nervosa
Women <65 years and men <70 years with a risk factor for osteoporotic fracture
- Fragility fracture
- Radiographic osteopenia or vertebral compression fracture
- Height loss (≥ 4 cm without record or ≥ 2 cm with a record)
- Taking medications associated with bone loss (glucocorticoids, aromatase inhibitors, or androgen deprivation therapy)
- BMI < 20 kg/m^2
- A history of parental hip fracture
Before starting osteoporosis drug and 1–2 years after treatment

7. Pharmacological management of osteoporosis

The indications for pharmacological therapy are shown in Table 9. Patients with osteoporosis should receive osteoporosis drugs, lifestyle modifications, and fall prevention protocols.

The recommendations for each osteoporosis drug are shown in Tables 10–15.

Bisphosphonates are recommended as an initial treatment for patients at high fracture risk and as an alternative treatment for patients at very high fracture risk who cannot use osteoanabolic agents. Fracture risk should be reassessed after 5 years of oral or 3 years of intravenous bisphosphonates therapy. A drug holiday should be considered to reduce the risk of atypical femoral fracture in patients with no history of fragility fracture and their T-scores increase to more than −2.5 (no longer at high fracture risk). Treatment can be continued for up to 10 years (oral form) or 6 years (intravenous form) in patients with a history of fragility fracture, BMD T-score of −2.5 or less after 3–5 years of therapy, or at very high fracture risk before treatment. Switching to another therapy can also be considered. Reinitiating osteoporosis medications after the drug holiday should be individualized. It may be considered in patients with a declining BMD T-score of −2.5 or less or experiencing a fragility fracture.

Denosumab is recommended as an alternative treatment for patients at high fracture risk and patients at very high fracture risk who cannot use osteoanabolic agents. Fracture risk should be reassessed after 5–10 years of therapy. Treatment can continue for up to 10 years if remaining at high fracture risk or very high risk before treatment. Educating patients on the importance of regularly receiving denosumab is essential to prevent the rebound phenomenon. Transition to potent bisphosphonates after denosumab discontinuation is recommended.

From the obstetrics and gynecology viewpoints, raloxifene and menopausal hormone therapy may benefit some selected patients at the postmenopausal clinic. Raloxifene may be an alternative treatment for postmenopausal osteoporosis with T-scores of −2.5 or less at the L-spine to reduce the risk of vertebral fractures. It may benefit postmenopausal women with risk factors for osteoporosis and breast cancer. Menopausal hormone therapy may be considered an alternative treatment for postmenopausal women at high fracture risk who age less than 60 years and less than 10 years past menopause. It also prevents bone loss in women with early menopause and should be continued for at least the mean age of natural menopause.

Table 7
Fracture risk categorization.

Fracture risk	Criteria
Low risk	**All of the following criteria** - No previous fragility fracture - T-score ≥ −1.0[a] - A 10-year probability of hip fracture < 3%[b]
Moderate risk	**All of the following criteria** - No previous fragility fracture - T-score between −1.0 and −2.5[a] - A 10-year probability of hip fracture < 3%[b]
High risk	**One of the following criteria** - A fragility vertebral or hip fracture - T-score ≤ −2.5[a] - T-score between −1.0 and −2.5 and a 10-year probability of hip fracture ≥ 3%[b] - T-score between −1.0 and −2.5 and a fragility fracture of the proximal humerus, pelvis, or distal forearm
Very high risk	**One of the following criteria** - Fragility vertebral or hip fracture within 12 months in patients ≥ 65 years with T-score ≤ −2.5 (IIa, B) - Recurrent vertebral fracture or vertebral fractures ≥ 2 levels with moderate to severe deformity (IIa, B) - Bilateral hip fractures, hip and vertebral fractures, or multiple fractures (≥ 3 times or ≥ 3 sites) (IIa, B) - Fragility fracture while on osteoporosis therapy for ≥ 2 years and no secondary cause of osteoporosis (IIa, B) - T-score ≤ −3.5 in women ≥ 65 years or men ≥ 70 years (IIb, D)

[a] T-score at the L-spine, femoral neck, total hip, or 1/3 radius.
[b] FRAX for Thai.

Table 8
Management according to fracture risk.

Recommendations for Management	Grading of recommendations	Quality of evidence
Low to moderate fracture risk		
Do not recommend osteoporosis drug	III	D
Adequate calcium and vitamin D intake and lifestyle modification	IIa	B
Re-evaluate fracture risk in 2–5 years	IIb	D
High fracture risk		
Bisphosphonate as the initial treatment, and denosumab as an alternative treatment	I	A
If inappropriate for bisphosphonate or denosumab, consider other antiresorptive drugs	I	A
If inappropriate for antiresorptive drugs, consider calcium and vitamin D supplements, lifestyle modification, and fall prevention	I	B
Monitoring treatment response - New fragility fracture - BMD measurement at 1–2 years after starting therapy	I	A
Very high fracture risk		
Sequential therapy - Teriparatide for 2 years → bisphosphonate or denosumab - Romosozumab for 1 year → bisphosphonate or denosumab	I	A
If unable to use an osteoanabolic drug, consider an injectable antiresorptive drug (zoledronic acid or denosumab)	I	A
If unable to use an injectable antiresorptive drug, consider oral bisphosphonate	I	A
Monitoring treatment response - New fragility fracture - BMD measurement at 1 year after starting therapy	I	A

Table 9
Indications for pharmacological therapy.

Indications for pharmacological therapy one of the following criteria)	Grading of recommendations	Quality of evidence
A fragility vertebral or hip fracture	I	A
T-score ≤ −2.5[a]	I	A
T-score between −1.0 and −2.5 and a 10-year probability of hip fracture ≥ 3%[b]	IIa	C
T-score between −1.0 and −2.5 and a fragility fracture of the proximal humerus, pelvis, or distal forearm	IIb	C

[a] T-score at the L-spine, femoral neck, total hip, or 1/3 radius.
[b] FRAX for Thai.

Teriparatide and romosozumab are recommended as initial treatments for patients at very high fracture risk. Treatments are 1–2 years for teriparatide and 1 year for romozosumab, followed by an antiresorptive drug (sequential therapy). They may be considered in patients with inadequate response to bisphosphonates despite good adherence for at least 2 years. Romosozumab is not recommended in patients with myocardial infarction or stroke within 1 year, and it must be discontinued if patients experience acute myocardial infarction or stroke during therapy.

8. Conclusions

The TOPF Clinical Practice Guideline for the Diagnosis and Management of Osteoporosis 2021 is a practical tool that assists

Table 10
Recommendations for bisphosphonate therapy.

Recommendations	Grading of recommendations	Quality of evidence
Initial treatment for patients at high fracture risk	I	A
Alternative treatment for patients at very high fracture risk who are unable to use osteoanabolic agents	IIa	A
Reassess fracture risk after 3–5 years of therapy	I	A
Consider a drug holiday if patients are no longer at high fracture risk (no history of fragility fracture and T-score > −2.5)	IIa	B
Consider reinitiating osteoporosis medications if declining in BMD or becoming a high fracture risk	IIa	B
Consider continuing treatment for up to 10 years (oral form) or 6 years (intravenous form) or switching to another therapy if remaining at high fracture risk or very high fracture risk before treatment	IIa	B

BMD: bone mineral density.

Table 11
Recommendations for denosumab therapy.

Recommendations	Grading of recommendations	Quality of evidence
Alternative treatment for patients at high fracture risk	I	A
Alternative treatment for patients at very high fracture risk who are unable to use osteoanabolic agents	IIa	A
Reassess fracture risk after 5–10 years of therapy	IIa	A
Consider continuing treatment for up to 10 years or switching to another therapy if remaining at high fracture risk or very high fracture risk before treatment	IIa	A
Educate patients on the importance of regularly receiving denosumab	I	B
Consider transition to potent bisphosphonates after denosumab discontinuation	IIa	B

Table 12
Recommendations for raloxifene therapy.

Recommendations	Grading of recommendations	Quality of evidence
Postmenopausal osteoporosis with L-spine T-score ≤ −2.5 and no risk of other fractures[a]	IIa	A
Alternative treatment for postmenopausal women at high fracture risk who are not appropriate to use bisphosphonate and denosumab	IIa	A
Prevention of bone loss in postmenopausal women with risk factor(s) for osteoporosis and breast cancer	IIa	A

[a] For reduction of vertebral fracture.

Table 13
Recommendations for menopausal hormone therapy.

Recommendations	Grading of recommendations	Quality of evidence
Alternative treatment for postmenopausal women at high fracture risk who are < 60 years and < 10 years past menopause	IIa	A
Prevention of bone loss in women with early menopause for at least to the mean age of natural menopause	IIa	C
Prevention of bone loss in postmenopausal women with risk factor(s) for rapid bone loss or osteoporosis	IIa	C

Table 14
Recommendations for teriparatide therapy.

Recommendations	Grading of recommendations	Quality of evidence
Initial treatment for patients at very high fracture risk[a]	I	A
Treatment for 1–2 years then, followed by antiresorptive drug	I	B
May consider in patients with inadequate response to bisphosphonates despite good adherence for ≥ 2 years	IIa	B

[a] For reduction of vertebral and nonvertebral fracture.

Table 15
Recommendations for romosozumab therapy.

Recommendations	Grading of recommendations	Quality of evidence
Initial treatment for patients at very high fracture risk[a]	I	A
Treatment for 12 months then, followed by antiresorptive drug	I	A
May consider in patients with inadequate response to bisphosphonates despite good adherence for ≥ 2 years	IIa	A
Do not recommend in patients with myocardial infarction or stroke within 1 year	III	B
Discontinue if patients experience acute myocardial infarction or stroke during therapy	I	B

[a] For reduction of vertebral, nonvertebral, and hip fracture.

healthcare professionals in diagnosing, evaluating, and managing osteoporosis in Thailand.

Conflicts of interest

The authors declare no competing interests.

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