

Review Article

Thai Osteoporosis Foundation (TOPF) position statements on management of osteoporosis

T. Songpatanasilp^{a,*}, C. Sritara^b, W. Kittisomprayoonkul^c, S. Chaiumnuay^d, H. Nimitphong^e, N. Charatcharoenwithaya^f, C. Pongchaiyakul^g, S. Namwongphrom^h, T. Kitumnuaypongⁱ, W. Srikam^j, P. Dajpratham^k, V. Kuptniratsaikul^k, U. Jaisamrarn^l, K. Tachatraisak^m, S. Rojanasthienⁿ, P. Damrongwanich^o, W. Wajanavisit^p, S. Pongprapai^q, B. Ongphiphadhanakul^e, N. Taechakraichana^l

^a Department of Orthopaedics, Phramongkutklao College of Medicine, Bangkok, Thailand

^b Nuclear Medicine Division, Department of Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

^c Department of Rehabilitation Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

^d Rheumatology Division, Department of Medicine, Phramongkutklao College of Medicine, Bangkok, Thailand

^e Endocrinology and Metabolism Division, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

^f Endocrinology and Metabolism Division, Department of Medicine, Faculty of Medicine, Thammasat University, Bangkok, Thailand

^g Endocrinology and Metabolism Division, Department of Medicine, Faculty of Medicine, Khonkean University, Khonkean, Thailand

^h Department of Radiology, Faculty of Medicine, Chiangmai University, Chiangmai, Thailand

ⁱ Rheumatology Division, Department of Medicine, Rajavithi Hospital, Bangkok, Thailand

^j Department of Rehabilitation Medicine, Faculty of Medicine, Thammasat University, Bangkok, Thailand

^k Department of Rehabilitation Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

^l Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

^m Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

ⁿ Department of Orthopaedics, Faculty of Medicine, Chiangmai University, Chiangmai, Thailand

^o Department of Orthopaedics, Police General Hospital, Bangkok, Thailand

^p Department of Orthopaedics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

^q Department of Rehabilitation Medicine, Vichaiyut Hospital, Bangkok, Thailand

Received 18 September 2016; revised 5 October 2016; accepted 6 October 2016

Available online 10 December 2016

Abstract

The adjusted incidence rate of hip fracture in Thailand has increased more than 31% from 1997 to 2006. Mortality and morbidity after hip fracture are also high. One year mortality after a hip fracture has increased from 18% in 1999 to 21% in 2007. The Thai Osteoporosis Foundation (TOPF) developed the first Clinical Practice Guideline (CPG) in 2002 and keeps updating the CPG since then. This latest version of the CPG is our attempt to provide comprehensive positional statement on the diagnosis, prevention and treatment of osteoporosis in Thailand. The study group who revised this position statement contains experts from the TOPF, Four Royal Colleges of Thailand, includes the Orthopaedic Surgeons, Gynecologists and Obstetricians, Physiatrists, Radiologists and 2 Associations of Endocrinologists and Rheumatologists which have involved in the management of patients with osteoporosis.

© 2016 The Korean Society of Osteoporosis. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: TOPF; Thailand; Management; Osteoporosis

* Corresponding author. Department of Orthopaedics, Phramongkutklao College of Medicine, Bangkok, Thailand.

E-mail address: thaweeps@yahoo.com (T. Songpatanasilp).

Peer review under responsibility of The Korean Society of Osteoporosis.

1. Epidemiology of osteoporosis and osteoporotic fractures in Thailand

According to the data in 2008, the life expectancy of the Thai population is 69.5 years for males and 76.3 for females [1]. Referring to the data from Population Research Center, Mahidol University, the life expectancy of Thai population has increased to 71.6 years for males and 78.4 years for females [2]. Surveys on the prevalence of osteoporosis in hospitalized Thai females at Thai governmental hospitals and random surveys of females in communities every region in Thailand in 2008 [3] and 2011 [4] indicate that if the WHO criteria for diagnosis of osteoporosis which indicates that bone density equal to or less than 2.5 SD of bone density in young adults ($T\text{-score} \leq -2.5$), an estimated 19–21% of females aged more than 40 years old will have lumbar spine osteoporosis and 11–13% will have femoral neck osteoporosis.

A study on incidence of hip fracture in 1997 in the Chiangmai province revealed that 268,139 people were aged over 50 years old (16.8% of the population) from a total of 1,443,245 subjects. 391 cases of hip fracture were found in this group. The average age was 74.4 years and the hip fracture incidence was higher in females than in males (2.1 times). According to this study, the incidence is 151.2 per 100,000 with adjusted incidence equaling 192.9 per 100,000 which is lower than USA, Japan, Hong Kong and Singapore but higher than China and Malaysia [5]. According to a study in 2006 conducted by the Thai Osteoporosis Foundation people aged over 50 years made up approximately 23% (381,204 of the total Chiangmai province population (1,658,298)). Overall, there were 690 people with hip fracture and an incidence of 181.0 per 100,000 or an adjusted incidence of 253.3 (male 135.9; female 367.9). The average age was 76.7 years. The incidence in females is 2.4 times higher than male. The most common cause of hip fracture was simple fall, accounting for 79% of the total. The incidence of hip fracture was low in people aged less than 60 years old. Nevertheless, a rapid exponential increase can be observed in people over 70 years old with the highest incidence group is in people 84 years and older (1238.9 per 100,000). It was found that 80% of hip fractures occurred in people over 70 years. Increased Hip fracture incidence in Thailand in 2006, 2025 and 2550 are expected to equal 23,426, 34,246 and 56,443 cases, respectively [6].

2. Osteoporosis related mortality and morbidity

1. Osteoporotic vertebral fractures are generally due to daily work without history of accidental injuries. Only 40% of females with a history of vertebral fracture are aware of their osteoporotic condition. These patients might have only mild to severe lumbar pain and in some cases, require hospitalization. However, in general, patients with osteoporotic vertebral fractures will result in significantly higher morbidity [7] and mortality [8] than those without fracture. Functional disability is related to the number of fractured vertebrae. More fractures result in higher

morbidity, mortality and also implies a higher risk of fractures of the left vertebra and hip [7–9].

2. Hip fracture is a common osteoporotic fracture with the most clinical complications. There is an extremely high mortality and morbidity due to bone fracture and loss of ability to perform daily life activities, respectively. In addition, management costs of hip fracture are significantly higher than treatment of fractures at other sites since patients are unable to walk. Furthermore, there are many complications for patients who do not receive proper corrective operations. A study indicating the mortality and morbidity after hip fracture in the Caucasian is as high as 20% in 1 year post-fracture and 30% of survivors will have permanent disability that requires intensive care from others or admission in nursing homes. It is found that 40% cannot walk or have to use walking aids and 80% cannot perform at least one activity that the patient could perform before fracture [10,11].
3. In Thailand, in 2010, the mortality of patients with hip fractures over a 10-year period was 367. According to the first incidence study in 1997 on hip fracture, death rates at 3, 6, 12, 24, 36, 60, 96 and 120 months were 10%, 14%, 18%, 27%, 32, 45%, 55% and 68%, respectively. The death rate after hip fracture is very high. During the first year, the death rate is 18% (female 16% and male 31%) and this rate is 8 times higher than that of general population. The death rate at 10th year is 68%. The median survival time is at 6 years (male 3 years, 6 months; female 7 years). Important factors contributing to high mortality rates include male sex, aged over 70 years and non-operative treatment of hip fracture [12]. According to a study from Maharat Nakhon Ratchasima Hospital in 2010, the mortality rate in patients with intertrochanteric fracture was as high as 23.6% in the first year. The mortality rate in patients receiving no operative treatment was 3 times higher than those receiving operative treatment [13].
4. In 2015, death rates and relating factors in patients with osteoporotic hip fracture were reported. According to the second study on incidence of hip fracture in the Chiangmai province in 2012–2013 [4], there was an increase in post fracture death rates. During the first year, the average death rate was 21.1%, 9.3 times higher than that of general population. The death rate at the 10th year was still 68%. The median survival time was 6 years (male 3 years and 6 months; female 7 years). The most important factors contributing to high mortality are 1) non-operative treatment (mortality rate is 4 times higher; Hazard Ratio = 1:0.27) 2) delayed operative treatment (patients receiving surgery at 1 week or more post fracture equals 4 times higher the mortality rate) 3) receiving no anti-osteoporotic drugs (mortality rate is 2 times higher; Hazard Ratio = 1:0.52 (0.30–0.87; $p = 0.004$)) [14].

2.1. Clinical assessment and screening

To screen for osteoporosis by axial DXA in general population is not recommended because it is not cost effective from

a medical economics standpoint. Nevertheless, at present, screening by OSTA [15] or KKOS [16] is suggested since it incurs no cost and the technique is a useful detection tool to determine the risk of osteoporosis for further BMD study.

Data and risk factors are recorded and 10-year probability of fracture are calculated by the FRAX™ <http://www.shef.ac.uk/FRAX/tool.jsp> [17] computer program. This 10-year probability calculation varies on nation and race. The program offers many nation-specific FRAX™ of several countries including to Thailand, which were approved by the Thai Foundation of Osteoporosis [18]. The 2 values: 10-year probability of hip fracture and 10-year probability of other major osteoporotic fractures are used for estimation of therapeutic threshold. For example, for patients in the USA with no fracture and BMD not less than -2.5 , the 10-year probability of fracture will be the value to determine the therapeutic threshold. If the patient has a 10-year probability of hip fracture $\geq 3\%$ or 10-year probability of other major osteoporotic fractures $\geq 20\%$, the start of drug treatment will be set [19].

3. Measurement of bone density

Bone mass density (BMD) can be measured by several tools including:

3.1. Dual energy X-ray absorptiometry (DXA)

The diagnosis of osteoporosis is based on the World Health Organization (WHO) criteria [20,21] in Table 1. Diagnosis depends on the comparison of measured BMD and maximum BMD in young female adult. Values less than or equal to -2.5 SD is the standard criteria for diagnosis of osteoporosis. The risk of bone fracture gradually increases from 1.4 to 2.6 times for each decreased SD [22].

To perform the bone density assessment for diagnosis of osteoporosis, it is suggested to examine lumbar spine by antero-posterior view and hip of non-dominant and non-fracture side by axial dual energy X-ray absorptiometry (axial DXA). It is not recommended to test for bone density at radius (peripheral DXA), with exception to severely obese patients over 130 kg, because it cannot examine and interpret bone density results from axial DXA or cases with primary hyperparathyroidism.

For diagnosis of osteoporosis in cases of lumbar, vertebra examination must include at least 2 vertebra. For the hip, femoral neck and total hip must be examined since these sites are related, providing predictive value for fracture.

In female, the value for comparison is an Asian female reference. Ideally, a Thai reference for Thai women should be used, however, in cases without appropriate Thai reference, Japanese or Chinese references can be used in general practice but not Caucasian reference.

In menopausal women or men over the age of 50 years, T-score is used to diagnosis osteoporosis. In premenopausal women or men younger than 50 years, the measured bone density must be compared with the standard deviation reference in age-matched female or male (Z-score, not T-score) in the same race and age group. The Z-score ≤ -2 SD is diagnosis as ‘below the expected range for age’ and Z-score > -2.0 SD is considered appropriate or ‘within the expected range for age’ [23,24].

Bone density measurement at lumbar, vertebra or hip can be used for follow-up treatment. The vertebra is the site that shows significant change in clinical study. However, in elderly with degenerative changes of spine, vertebral fracture or calcified aorta, the measurement at total hip BMD will have less error in clinical follow-up.

Measurement of bone density by DXA should be done by radiological technician with proper quality control and quality assessment.

3.2. Indication for axial DXA measurement

1. Female aged over 65 years and male aged over 70 years [6].
2. Early menopause (before 45 years including bilateral oophorectomy).
3. Hypoestrogenism for more than 1 consecutive year before menopause (receiving GnRH, prolonged intensive exercise, chronic illness) with the exception of pregnancy and breastfeeding.
4. Prolonged glucocorticoid administration (daily prednisolone 7.5 mg or equivalent for at least 3 consecutive months).
5. History of fraternal or maternal hip fracture [25].
6. Menopausal women with body mass index less than 20 kg/m^2 [26].

Table 1
Diagnosis of osteoporosis based on the World Health Organization criteria.

Diagnosis	Findings
Normal	Bone density within normal limit, value more than or equal to -1 SD when compared to average bone mass of puberty woman (T-score ≥ -1)
Osteopenia	Bone density within normal limit, value between -1 and -2.5 SD when compared to average bone mass of puberty woman ($-2.5 < \text{T-score} < -1$)
Osteoporosis	Bone density within normal limit, value equal to or less than -2.5 SD when compared to average bone mass of puberty woman ($-2.5 < \text{T-score} < -1$) (T-score ≤ -2.5)
Severe/established osteoporosis	Bone density within normal limit, value equal to or less than -2.5 SD when compared to average bone mass of puberty woman (T-score ≤ -2.5) and with fragility fracture

7. Menopausal women with decreased height of at least 4 cm [27].
8. Female receiving treatment by aromatase inhibitors [28] or male receiving treatment by androgen deprivation therapy [29].
9. Radiographic osteopenia and/or vertebral deformity by X-ray [9].
10. History of fracture from low-energy injury [30].
11. FRAX[®] assessment for risk of fracture, specific for Thai population, with non BMD approach result showing 10-year probability of fracture in intermediate risk [31].
12. Rated in intermediate group by OSTA score [11], KKOS score [12] or risk from nomogram (probability) is equal to or more than 0.3 for menopausal women [32].

(Note; OSTA; Osteoporosis Self-Assessment Tool for Asians, KKOS; Khon Kaen Osteoporosis Study score).

3.3. BMD change and least significant change, LSC [27]

As measurement can sometimes be skewed, there too can be an error in measurement of bone density. Hence, it is necessary to judge the least magnitude of change that can be guaranteed that it is not an error.

For the calculation of least significant change (LSC), the International Society for Clinical Densitometry (ISCD) suggests the measurement of bone mass in 30 patients 2 times at each site or 15 patients 3 times at each site. In each measurement, the patient must stand and exit the analyzer for re-posturing. The collected data must be calculated for root mean square standard deviation (RMS-SD) and/or root mean square coefficient of variation (RMS-%CV). The two values are accepted as precision error for the calculation of LSC. The LSC is the upper limit of the 95% confidence interval and precision error is calculated with the following formula:

$$\text{LSC} = 2.77 \times \text{Precision error}$$

If the change of bone mass is more than LSC, there will be 95% confidence that the change is an actual change. Changes less than this level do not indicate that there is an actual decrease or increase of bone density, since it is lower than precision error which can occur without any actual change.

A convenient and feasible calculation spreadsheet is available to be downloaded free of charge at www.iscd.org/resources/calculators/. It is suggested that each institute should find individual LSC from individual precision error.

4. Biochemical markers of bone turnover: BTMs

Biochemical markers of bone turnover (BTMs) are not recommended for diagnosis of osteoporosis because there are many confounding factors. BTMs can also change several in non-osteoporosis associated conditions. However, BTMs can be used along with BMD for risk assessment for fracture [33–35]. BTMs, however, can be useful for follow-up [36].

It is recommended that BTMs should be tested at 3 months and 1 year. These markers can prove to be accurate and efficient in monitoring drug response.

Common BTMs include urinary deoxypyridinoline (DPD), urinary N-telopeptide (NTx) and serum C-telopeptide (CTx). Common biomarkers for bone construction include bone specific alkaline phosphatase (BSAP), osteocalcin, C-terminal propeptide of type 1 procollagen (P1CP) and N-terminal propeptide of type 1 procollagen (P1NP) [37].

4.1. Laboratory investigations for osteoporotic patients

4.1.1. Aims of laboratory investigation

1. Confirm diagnosis of osteoporosis
2. Assessment of risk for fracture
3. Finding secondary causes of osteoporosis

In general, osteoporotic laboratory investigation to identify the cause of osteoporosis depends on history taking and physical examination results for each patient. Nevertheless, the recommendation for routine laboratory investigation is as follows: [38]

- Complete blood count (CBC) and erythrocyte sedimentation rate (ESR) to assess for anemia. A condition such as multiple myeloma might cause osteoporosis.
- Calcium, phosphate and albumin for diagnosis and differential diagnosis of osteomalacia and secondary osteoporosis and pre-treatment evaluation.
- Liver enzymes including alanine transaminase (ALT or SGPT) and aspartate transaminase (AST or SGOT) because chronic liver disease could lead to osteoporosis.
- Alkaline phosphatase to assess other diseases that can cause osteoporosis and osteomalacia.
- Kidney function test including blood urea nitrogen (BUN), creatinine and calculation of glomerular filtration rate (GFR) or creatinine clearance for evaluation of renal function before treatment.
- Lateral thoraco-lumbar spine X-ray for evaluation of non-clinical fracture or antero-posterior hip X-ray if indicated.

Other laboratory investigations are used for specific cases and to find secondary osteoporotic causes. The indications are:

1. Suspicious history for any other disorders that can cause osteoporosis
2. Physical examination revealing abnormalities that might be the cause of osteoporosis
3. Female osteoporosis or fracture that is not related to menopause or old age
4. Male osteoporosis

Investigation of cause of osteoporosis must relate to history and physical examination as the following:

- Thyroid stimulating hormone (TSH)
- Parathyroid hormone (PTH)
- 24 h urine calcium and sodium
- Serum protein electrophoresis
- 25-hydroxyvitamin D (25(OH)D)
- Sex hormones: estradiol, testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
- Prolactin
- Growth hormone
- Urine free cortisol or low dose dexamethasone suppression test
- Fasting plasma glucose

4.2. Pharmacological prevention

4.2.1. Menopausal Hormone Therapy: MHT

According to the consensus among national and international organizations and societies about menopause, hormone use is recommended for prevention of osteoporosis-related fractures. Hormone therapy is also an effective and appropriate treatment for women under the age of 60 or women experiencing menopause for less than 10 years [39]. For MHT, the principles are:

1. Women Health Initiative (WHI) study [40] reported the use of conjugated equine estrogen (CEE) with medroxy progesterone acetate (MPA) for 5 years and found that this regimen can reduce the incidence of vertebra fracture and hip fracture with clinical symptoms by 34% and other bone fractures by 23%.
2. MHT should be considered for each individual case. This consideration should include: quality of life, importance of health problem, age, duration of menopause, risk of venous thromboembolism, stroke, ischemic heart disease and breast cancer.
3. Dosage and period of hormone treatment must be considered case by case and depends on the target and safety in treatment.
4. In cases with premature ovarian insufficiency (POI), systemic MHT is suggested for at least a period until the expected natural age of menopause.
5. It is not recommended to use bio-identical hormone.
6. Hormone cessation can result in 3%–6% annual bone mass loss. It is evidenced that after cessation of hormone, the benefit of hormone in reducing of risk of fracture rapidly disappear (catch-up phenomenon) and the incidence of fracture will increase to the same level as that of the general population who do not receive hormone therapy within a 1-year period after cessation of hormone [41]. Therefore, careful consideration is suggested in hormone supplementation therapy.
7. Present available evidences do not support the use of hormone therapy in patients with history of breast cancer or with high risk for breast cancer.

4.3. Non-pharmacological prevention

The present strategies for prevention of osteoporosis focus on non-pharmacologic strategies for its cost effectiveness. There are 4 main methods:

- Food and nutrition
- Exercise
- Lifestyle modification
- Prevention of fall

4.3.1. Nutrition for prevention of osteoporosis

Important nutrients responsible for constructing and repairing bone include: protein, vitamin C, vitamin K and minerals (magnesium, copper, zinc and phosphorus). Of these nutrients; calcium, vitamin D and vitamin K are most essential. Other nutrients including magnesium, copper, manganese and phosphorus are usually not deficient in general population except in cases with chronic alcoholism and intestinal abnormalities.

Calcium: The daily requirement of calcium is different in different age groups. According to the recommendation of the Thai Ministry of Public Health in 2006, the recommended amount is 800–1000 mg/day [42]. It is suggested that adequate intake is better than using calcium supplementation.

Vitamin D: Collaborates with hormone in homeostasis of calcium and phosphate in human body. It reacts by increasing intestinal absorption of calcium and phosphorus. It also co-works with parathyroid hormone (PTH) in normalizing blood calcium and phosphate. To add, vitamin D plays an important role in bone construction and bone mineralization. The daily requirement of vitamin D is 5–15 mcg/day (600–800 IU/day) [42], which is the appropriate level for prevention of vitamin D deficiency in each age group.

Risk factors for vitamin D deficiency includes:

- Decreased skin ability to synthesize 7-dehydrocholesterol in the elderly
- Less sunlight exposure
- Decreased renal function resulting in decreased synthesis of 1,25(OH)₂D
- Malabsorption
- Low intake of vitamin D nutrition

Protein: Excessive protein intake (more than 2.0 g/kg/day) increases the risk of osteoporosis and fracture [43] because it induces calcium excretion via urination. Too little protein intake (less than 0.8 g/kg/day) can reduce intestinal calcium absorption which can result in increased parathyroid hormone secretion that further results in calcium bone resorption [43,44]. The adequate amount of protein intake is not more than 1.0–1.5 g/kg/day which will not disturb calcium metabolism and bone density [44]. There is a relationship between protein intake and bone density in cases where protein is taken along with calcium and vitamin D [45].

Vitamin K: There are 2 kinds of natural vitamin K: vitamin K-1 (phylloquinone) from plant and vitamin K-2 (menaquinone) which is synthesized in the colon of animals. There are high contents of vitamin K in green vegetables but little amounts are found in fruits and cereals. The average amount of vitamin K is found in meat and milk. Bacteria in human colon can synthesize vitamin K-2 or menaquinone. However, the absorption of vitamin K at colon is done by passive diffusion and the derived amount is usually not adequate.

Osteoblast can generate a collagen matrix and osteocalcin which is a non-collagen matrix with vitamin K. The newly formed osteocalcin is the main core for mineralization. Hence, the finding of increased undercarboxylated osteocalcin (ucOC) implies low vitamin K levels or vitamin K deficiency which might result in mineralization problems. The increased ucOC can be a predictive parameter for hip fracture in elderly female. One Thai study reports that ucOC at 2.314 ng/mL [46] is the cut off for vitamin K deficiency and elderly females in this study have high prevalence, 39.1%, of vitamin K deficiency (or ucOC > 2.314 ng/mL) and elderly with ucOC of more than 2.314 ng/mL will have less bone masses at ultra-distal radius and distal 1/3 of radius, also 25(OH)D levels were significantly less than those of the elderly with normal ucOC ($p < 0.05$).

Other nutrients: Magnesium, copper, zinc, manganese and phosphorus are normally not deficient in normal population except in cases with gastrointestinal problems such as chronic alcoholism and intestinal abnormality.

4.3.2. Exercise in postmenopausal women

4.3.2.1. Weight bearing exercise with resistance muscle exercise. Weight bearing exercise with resistance muscle exercise 30–40 min per day for 3–4 days per week can reduce bone loss at the vertebra and hip [47–49]. Exercise modification should be adjusted to fit with physical limit. Progressive resistance exercise of leg muscle can help reduce/delay bone loss of hip [47]. Walking alone cannot reduce or delay bone loss of vertebra in menopausal women, but it can help or delay bone loss of hip [49,50].

International Osteoporosis Foundation (IOF) suggests an exercise program [51] that can effectively stabilize bone mass of menopausal women with low bone mass aged 48–60 years old. Different types of exercise should include high-impact weight bearing and progressive resistance varieties, beginning at 60%–80% activity level with a one repetition maximum 4 days per week. Exercise regimens can either last 60 min 2 days per week at a fitness club or 25 min, 2 days per week at home.

4.3.2.2. Exercise for increased strength of back extensor. The incidence of collapsed vertebra in patients over 40 years old is 20% [52]. It was more commonly found among patients who have weaker back extensor muscles than those with strong back extensor muscles. Therefore, adequate exercise, 5 days per week for 2 years, is recommended to increase strength of

back extensors. This can help reduce compression fractures of spine by more than 50% and effects can last for 8 years after exercise discontinuation [53].

4.3.2.3. Exercise for prevention of fall. To prevent falls, balance training and lower limb strengthening is recommended [54]. There are many different balance training exercises. The National Institute of Aging [55] suggests to structure workouts of 2 sets of 10 repetitions per day at least 3 days per week. The workout program should begin with basic posture training movements including using the finger to touch a chair. If this action can be done, retry the same action with eyes closed and without using the finger as a guide for at least 15 s.

Tai chi, Qi qong, walking exercises, jogging and ballroom dancing are also considered balance training. Practicing Tai chi for 5 min, 2 routines per day every day for 4 months can help reduce falls by 50% [56].

4.3.2.4. Exercise when there is osteopenia [57]. Low-impact weight-bearing exercises such as walk daily for 40 min 3 days per week or 30 min per day every day, Tai chi, ballroom dancing, pole dance, etc are recommended.

To increase muscle strength, weight lifting of no more than 20 pounds (10 kg) 3 days per week is recommended. Weight that passes through wrists, vertebra and hips can help increase bone mass in those bones. Back extensor exercises, balance training and postural training are all essential to prevent further loss of bone mass.

4.3.2.5. Exercise when there is “Osteoporosis” [57]. Recommended exercises for patients with osteoporosis are the same as for osteopenia with the exception of muscle strengthening exercises, which are prohibited. The International Osteoporosis Foundation (IOF) suggests an exercise program for patients with osteoporosis [58] to begin by warming up the muscles with adequate stretching and walking following by cardiovascular exercise to increase muscle strength, posture training and cool down at the end.

4.3.3. Effect of exercise

Weight bearing exercise can help increase bone mass but it must be continued for 9–12 months [59]. According to a meta-analysis, it concluded that consistent exercise can help delay the decrease of bone mass in menopausal age [60].

Progressive resistance strengthening of leg muscle effectively helps prevent reduction of bone mass of femur [49].

Weight bearing exercise with progressive resistance strengthening of leg muscle effectively helps prevent reduction of bone mass of vertebra [49]. A systematic review and meta-analysis [61–63] showed that balance training and progressive resistance strengthening of leg muscle reduces the risk of fall by 29–49% in the elderly.

The specific type of exercise that is proven most useful in postural stabilization and preventing fall is Tai-chi with a 47.5% decrease of re-falling [56].

4.3.4. Precautions of exercise in osteoporotic patients [64]

It is suggested to avoid strenuous exercises such as high impact aerobic dance, heavy weight lifting, running, mountain biking, which could all increase the risk of fracture in patients with underlying osteoporosis. In addition, inappropriate running should be avoided in cases with underlying degenerative knee or hip since running is 1–2 times more weight bearing on both knee and hip.

Back bending and body twisting in daily activities and exercise such as bending to lift objects, playing golf and sits-up should be avoided. Weight lifting is not appropriate for patients with recent vertebral fracture but allowable in those with chronic back pain. Swimming and underwater exercises have no effect in prevention or treatment of osteoporosis.

If symptoms of aching muscle present after exercise for more than 2 days, it is recommended to stop exercising until the pain is relieved. Only until then should exercise be resumed with decreased weight.

4.4. Life-style modification

- Smoking cessation
- Avoid coffee and caffeinated beverages
- Avoid salty foods and high protein diet
- Limit alcoholic drinking
- Increase physical activities
- Control chronic diseases that present risk for osteoporosis
- Avoid drugs that induce osteoporosis

5. Fall prevention

Falling is a serious problem that can cause fracture in the geriatric population. Falls occur in one-third of the elderly aged over 65 years and a half of the elderly over 80 years old [65]. Any patient with history of falling more than twice a year should be assessed for risk factors of fall.

5.1. Risk factors of fall

Fall is usually related to several factors. Fall rates will increase from 8 to 10% in patients without risk to 69–78% in patients with 4 or more risks [66,67]. According to a study on risk factors by multivariate analysis, there are only 3 important risks for fall including hip muscle weakness, postural loss and number of medication [68]. These risk factors are divided into 2 main groups.

Intrinsic factors

- History of fall
- Nutritional deficiency
- Impaired sensory function
- Impaired vision
- Unstable walking
- Multiple medication
- Personal illnesses such as diabetes mellitus, cerebrovascular disease related paralysis, foot problem, postural hypotension, etc.

- Muscle weakness/postural defect
- Fear of all

Extrinsic factors

- Environment such as obstructed floor surfaces, wet floor, toilets without support rails, limited lighting etc.
- Clothes and shoe use
- Improper walking aids

5.2. Fall Risk Assessment

Risk assessment for fall can be assessed by several tools including the Hendrich II Fall Risk Model [69], Morse Fall Scale [70], Falls Risk Assessment Tool (FRAT) [71], Falls Risk Assessment Score (FRAS) [72], Fall Risk Assessment and Screening Tool (FRASST) [73]. To assess the posture skill, the tools are timed up and go test [74,75], chair stand test [76], functional reach [77], single leg stance [78] and Tandem stance.

5.3. Fall prevention strategies

Finding at-risk groups can be done either by interview, review of medication or with risk and posture skill assessment tools. It is reported that the use of drugs with central nervous system (CNS) effect can increase the risk of fall by 10 times (OR 9.9, 95% CI; 1.6–60.63) [79]. Special precautions are needed for sedatives, hypnotics, anti-depressants and benzodiazepine [80]. Use of these drugs can increase the risk of fall. It is recommended that the least number of drugs should be used as indicated and at appropriate dosage.

Exercises that are proven methods to prevent fall [81] include muscle strengthening, postural training and Tai chi. These exercises are useful to promote formation and strengthening of bone and muscle. Balance improvement is also helpful for preventing fall.

To prevent fall, a number of issues including foot and shoe problems, environmental settings (of lighting, floor hazards etc.) and vision impairment must be assessed and resolved. Any of these issues, if left unresolved, could lead to a disturbance of posturing and may result in increased possibility of fall [82]. Hip protection devices do not decrease the risk of fall but can reduce the impact force if fall occurs. According to a meta-analysis in 2010 on 13 publications covering 11,573 patients, it was found that the tool could possibly reduce the hip fracture rate in hospitalized osteoporotic elderly patients [83]. A major concern for the tool is the compliance of long-term wearing. Hence, adequate education for patients and care takers is important. Topic suggestions include knowledge on the risk for falling, limitation of daily activities, need for slowing in postural change and familiarization with living environment.

Daily vitamin D dosage of 700–1000 IU or 17.5–25 µg per day [84] can help reduce the risk of fall (odds ratio 0.86, 95% CI; 0.77–0.96). This result is clearly seen in the patients of

vitamin D deficiency and seen in studies of concomitant use of vitamin D and calcium [85].

6. Goals of osteoporosis treatment

There are three main goals for osteoporosis treatment, which are based on the following priorities:

1. Reducing the chance or risk for osteoporotic fracture.
2. Reducing or stopping high bone loss and promoting construction of bone mass in order to decrease the possibility for fracture and strengthening of bone.
3. Improving patient quality of life.
 - Pain reduction.
 - Maintaining normal or near normal body movement.
 - Increasing self-help ability in daily activity or decreasing dependency.

6.1. Indications for pharmacological treatment of osteoporosis

6.1.1. Indications in postmenopausal osteoporosis (PMO) and male idiopathic osteoporosis (MIO)

For menopausal women and men aged over 50 years old, treatment is needed one of these indications is present:

1. Vertebral fracture of hip fracture from low-energy injuries.
2. Female age more than 65 years and male aged more than 70 years with bone density test from standard axial DXA at lumbar spine BMD or femoral neck BMD or total hip BMD showing T-score ≤ -2.5 .
3. Results from 10-year probability of hip fracture by FRAX™ using Thai reference (with BMD or without) $\geq 3\%$.

6.1.2. Specific indications in cases of female with cancer treatment induced osteoporosis and males with prostate cancer and received Androgen Deprivation Therapy

Indications for women with cancer treatment induced osteoporosis and men with prostate cancer received Androgen Deprivation Therapy include:

1. Vertebral fracture of hip fracture from low-energy injuries.
2. Female age more than 65 years and male aged more than 70 years with bone density test from standard axial DXA at lumbar spine BMD or femoral neck BMD or total hip BMD showing T-score ≤ -2.5 .
3. Results from 10-year probability of hip fracture by FRAX™ using Thai reference (with BMD or without) $\geq 3\%$.
4. Female aged less than 65 years requiring aromatase inhibitors with T-score of bone density measured by axial DXA, lumbar spine BMD or femoral neck BMD or total hip BMD ≤ -2.5 .
5. Male aged less than 70 years requiring Androgen Deprivation Therapy with T-score of bone density measured by

axial DXA, lumbar spine BMD lumbar spine BMD or femoral neck BMD or total hip BMD ≤ -2.5 .

6.2. Guidelines for drug selection for treatment of osteoporosis

To select a drug for treatment of osteoporosis, practitioners should be concerned about drug action, ability to reduce fracture risk reported in clinical trials in human, potential adverse events and most importantly, tailored therapy for each individual patient since different drugs may suit different patients. As a result, there is no recommendation for first line drug. The physician in charge must determine appropriate treatment for each patient. Decision making must be aimed at the treatment objective of fracture prevention. Therefore, proper consideration of treatment requires the consideration of drug efficacy to reduce osteoporotic fracture (anti-fracture efficacy), safety in short and long-term uses and cost-effectiveness from a Thai medical economics viewpoint. The following is a list of available drugs:

6.2.1. Bisphosphonates

Guidelines for bisphosphonate use are as follows:

- Once daily oral Alendronate [86,87] and Risedronate [88–90] can increase bone density and decrease the risk of vertebral fracture, hip fracture and non-vertebral fractures. These drugs are recommended for postmenopausal women and men with osteoporosis.
- Once weekly oral Alendronate and Risedronate [91,92] can help increase bone density and decrease the risk of fracture which is similar to once daily forms but can increase patient compliance. Weekly oral Alendronate or Risedronate plus vitamin D (2800 unit or 5600 unit per tablet) [93,94] has the same efficacy as once daily Alendronate and Risedronate administration.
- Once monthly Risedronate can increase bone density and decrease risk of bone fracture similar to once weekly use and can increase patient compliance.
- Once daily Ibandronate can increase bone density and decrease risk of vertebra fracture. Efficacy in reducing the non-vertebral fracture is evidenced from a study Ibandronate use in patients with hip bone density T-score less than -3.0 [95] with once monthly oral regimen [96] and trimonthly injection regimen [97]. It was found that Ibandronate could increase bone density and decrease the risk of vertebral fracture similar to once daily regimen and can also increase patient compliance.
- Once a year Zoledronic acid intravenous injection can increase bone density of vertebra, reduce risk of fracture at vertebra, hip and other bone in postmenopausal women [98,99] and men with osteoporosis and reduce mortality rates in patients with operable hip fracture [100].
- Since bisphosphonates is excreted via kidney, it is contraindicated in any patient with glomerular filtration rate (GFR) less than 30 mL/min (in case of oral form) and 35 mL/min (in case of injection form).

- There are evidences that bisphosphonates increases risk of osteonecrosis of the jaw and atypical femoral fracture, which depends on dosage and duration of use [101,102].

6.2.2. Strontium ranelate

- Strontium ranelate can increase bone density, decrease risk of vertebral fracture and non-vertebral fracture. About the hip fracture, strontium ranelate can decrease risk of hip fracture in subgroup of postmenopausal women aged over 74 years with hip bone density (FN T-Score) < -3.0 [103,104].
- Strontium ranelate can increase bone density in men with osteoporosis as in postmenopausal women, therefore, it is recommended as an alternative treatment for male patients with osteoporosis.
- Contraindications for Strontium ranelate [105] in the following patients:
 - Patients with history or present illness due to ischemic heart disease, peripheral arterial disease and cerebrovascular disease.
 - Patients with history or present illness due to venous thromboembolism including deep vein thrombosis and pulmonary embolism.
 - Patients with history or present illness due to permanent and non-permanent immobilization including bedridden status.
 - Patients with uncontrolled hypertension.

6.2.3. Denosumab

- This drug is indicated for treatment of osteoporosis in postmenopausal women with high risk of fracture. It can decrease the incidence of vertebral, hip and non-vertebral fractures. Hence, it is mainly used for treatment of osteoporosis in postmenopausal women [106,107].
- There are strong evidences supporting that this drug can increase bone density of lumbar vertebra, hip and radius in postmenopausal women. It can increase bone density in men with osteoporosis. This drug is recommended for both postmenopausal women and men with osteoporosis.
- Denosumab can prevent bone mass loss in women with breast cancer receiving aromatase inhibitor and can prevent bone mass loss in men with prostate cancer receiving Androgen Deprivation Therapy with high risk for fracture.
- This drug is recommended for treatment of osteoporosis by subcutaneous injection every 6 months and there is no requirement of decreasing dosage in patients with impaired renal function [106].
- There is a precaution for patients with risk of hypocalcemia.
- There are evidences that this drug can increase the risk of skin infection and might induce skin rash and dermatitis. It is recommended to monitor these potential problems in any patient receiving this drug. Regarding osteonecrosis of the jaw and atypical femoral fracture, lower incidences have been found when compared to bisphosphonate [107].

6.2.4. Raloxifene

- Raloxifene can prevent loss of bone mass and reduce the risk of vertebral fracture in postmenopausal women with osteoporosis [108].
- It can reduce the risk of breast cancer in women with osteoporosis. The effectiveness is comparable to tamoxifen in prevention of female breast cancer in risk group [109].

6.2.5. Menatetrenone

- Menatetrenone might be useful for patients with high ucOC levels. It can prevent bone loss and reduce the risk of vertebral fracture [110,111] and repeated vertebral fracture in patients with previous history of at least 5 sites of vertebral fractures [112].

6.2.6. Teriparatide

Teriparatide (PTH 1-34) is used for subcutaneous injection. This drug can help increase bone density and decrease the risk of vertebral fracture and non-vertebral fracture in patients with previous history of vertebral fracture in both postmenopausal women and elderly men [113,114].

6.2.7. Specific indication for teriparatide or parathyroid hormone 1-34

- Since teriparatide is expensive and requires no longer than 2-year period of use, more specific criteria and stricter indications are needed comparing to others [114]. It is indicated for severe osteoporosis, high risk of repeated fracture or failure from bisphosphonates use and the patient must be older than **65 years** and with one of these criteria.
 1. Diagnosis of severe osteoporosis with fracture or history of fractures with the following characteristics:
 - Vertebral Compression Fractures at more than 2 sites and BMD T-Score ≤ -3.5 at spine or hip (either femoral neck or total hip) or
 - Non-vertebral Fracture at more than 2 major bone sites including upper and lower extremities, pelvis (excluding small bones in hand and foot, clavicle and scapula) accompanied with BMD T-Score ≤ -3.5 at spine or hip (either femoral neck or total hip) or
 - Vertebral Compression Fractures at 1 site with Non-vertebral Fracture at 1 major bone site and BMD T-Score ≤ -3.5 at spine or hip (either femoral neck or total hip).
 2. Reliable evidence of inadequate-response to bisphosphonates [115,116] according to all of the following criteria:
 - New vertebra fracture at 1 or more sites or further collapse of previous fracture vertebra or new non-vertebral fracture (considered low-energy injury fracture) at least 1 site despite during bisphosphonate treatment for 2 years or more years.

- Equal to or more than 3% decrease of BMD of lumbar vertebra in two comparable tests or equal to or more 5% decrease of femoral neck or total hip BMD in two comparable tests by calculation from Least Significant Change (change more than LSC) (see information previously described in diagnosis by BMD) after bisphosphonate treatment for more than 2 years.
 - Patient evaluation of good adherence to bisphosphonate treatment.
3. Use in patients with Atypical Femoral Fracture (AFF) (either complete or incomplete form) (see guideline for diagnosis and treatment according to ASBMR recommendations [102]) with expectation to improve union of fracture [117–121]. It is suggested to stop previous use of any anti-resorptive drugs during teriparatide use.
- After teriparatide injection, patients may experience a transient increase of blood calcium level by 0.8 mg/dL. Highest levels can be seen 4–6 h after injection and will steadily decrease to pre-injection level. Most patients have normal blood calcium level. Transient hypercalcemia can be seen in 11% of patients receiving teriparatide injection and only 3% have persistent hypercalcemia at rechecking [113].
 - Before using teriparatide, confirmation of the following is required:
 - The patient has no previous hypercalcemia or hyperparathyroidism.
 - The patient has no malignancy or history of cancer within the past 5 years, no diseases with high risk or bone cancer such as Paget's disease of bone or history of radiation treatment at bone.
 - It is not recommended in any patients whose bone growth plate is still open.

7. Guideline for calcium and vitamin D administration for patients with osteoporosis

Patients need adequate intake of calcium and vitamin D either with anti-osteoporotic agents or non-pharmacological treatments. Both may be derived from food intake, exposure to sunlight or calcium and vitamin D supplementation.

7.1. Calcium

- Calcium intake is recommended through diet since it is safe, inexpensive and can reduce bone fracture. Patients with insufficient calcium dietary intake should consider calcium supplementation.
- There are clinical evidences that calcium with vitamin D can reduce osteoporotic fracture [122].
- National Osteoporosis Foundation [123] and Institute of Medicine (IOM) [124] suggest that men aged 50–70 years should intake 800–1000 mg of calcium per day. Women and men over the age of 51 and 71 years, respectively should intake 1000 mg of calcium daily. There is no evidence that receiving calcium more than the recommended level will result in any increased advantage to bone.

- Receiving more than 1200–1500 mg of calcium per day increases the risk of stone formation, cardiovascular and cerebrovascular diseases. However, this issue is still a controversial issue.
- In general, calcium carbonate is used because it is cost effective. However, calcium carbonate might have some unwanted on gastrointestinal side effects such as constipation, flatulence and bloating. Intake with meal can help reduce unwanted effects and increase calcium absorption [125,126]. For appropriate calcium absorption, the amount of calcium should not exceed 500–600 mg at a time. Divided dosage is recommended for patients that require more than 600 mg/day [125,126].
- Calcium citrate can be absorbed regardless of gastric pH, therefore, it is suggested for patients with underlying achalasia to reduce unwanted gastrointestinal side effects [125,126].

7.2. Vitamin D

7.2.1. Assessment of vitamin D status in human body

To assess vitamin D status, the 25(OH)D test is suggested. At present, the 1,25(OH)₂D test is available but not recommended because 1,25(OH)₂D is not sensitive enough to determine vitamin D deficiency [127,128].

7.2.2. Normal value of 25(OH)D

For 25(OH)D, vitamin D deficiency is judged at different levels according to US Institute of Medicine (IOM) and US Endocrine Society (Table 2). IOM will focus on general population whereas the Endocrine Society will focus on risk groups.

7.2.3. Indication for measurement of vitamin D status [132]

- 25(OH)D is not indicated for general population.
- Patients with osteoporosis or osteoporotic fracture, 25(OH)D is indicated that reduced incidence of bone fracture can be achieved with more than 30 ng/mL treatment 25(OH)D. Institutes or hospitals that are unable to perform 25(OH)D test administer delayed active vitamin D treatment instead.

7.2.4. Recommendations for the vitamin D deficiency in Thai population

- 25(OH)D is not indicated for general population but recommended for specific patients with osteoporosis.
- Cut-off level of 25(OH)D is less than 20 ng/mL to indicate vitamin D deficiency.
- A minimum of 30 ng/mL 25(OH)D to maintain the highest efficacy of antiosteoporotic drugs.
- To prevent vitamin D deficiency, adults under 70 years should intake at least 600 IU vitamin D daily. Those over 70 years should least intake 800 IU calcium daily [132].
- Patients requiring 25(OH)D > 30 ng/mL should intake at least 800 IU vitamin D each day.

Table 2
Classification of vitamin D status based on blood 25(OH)D levels.

US Institute of Medicine			US Endocrine Society		
Vitamin D status	ng/mL	nmol/L	Vitamin D status	ng/mL	nmol/L
Increased risk of deficiency	<12	<30	Deficiency level	<20	<50
Increased risk of insufficiency	12–19	30–49	Insufficiency level	20–30	50–75
Adequacy	20–50	50–125	Sufficiency level	>30–100	>75–200
Increased risk of excess	>50	>125	Toxic level	>100	>250

- Sunlight is an important source of vitamin D. Those who cannot gain adequate exposure to sunlight will need vitamin D supplementation.
- Vitamin D2, vitamin D3 or natural vitamin D should be inactive form at first. This active form (calcitriol) or semi-active form (alfacalcidol) is indicated only in patients with renal failure or liver failure [132]. Blood and urine calcium monitoring is required as adverse effects are hypercalcemia and hypercalciuria.

8. Follow-up and assessment of treatment

8.1. Assessment of drug response

Assessment of osteoporotic drug is required to measure the efficacy of fracture reduction. At present, there is still no drug with zero risk (no fracture at all). If incidence of fracture during medication is present, patient drug response, either positive or negative, cannot be concluded. Many evidences are required at time of assessment which can be conducted with 2 methods:

8.1.1. Measurement of BMD by DXA

BMD should increase or not decrease when compared to pre-medication. Interval between two tests should not be within 1 year and conducted by the same axial DXA analyzer. There are some possible errors in measurement of BMD by axial DXA. Measurement error may be present if lumbar spine BMD from 2 assessments decrease $\geq 3\%$ each year or if total hip BMD or femoral neck BMD decreases $\geq 5\%$ [115,116] each year. And is more than LSC value (as previously described in diagnosis by BMD). Receiving treatment for more than 1 year implies that BMD actually decreased resulting in probable inadequate patient response. If the decreased BMD does not exceed the aforementioned criteria, the drug is still considered effective. However, if a fracture occurs during treatment with decreased BMD exceeding the mentioned criteria, it is considered inadequate patient response and the drug will need to be changed accordingly.

8.1.2. Assessment by BTMs

If the drug can prevent bone loss, bone resorption markers should decrease. And if the drug activates the formation, a bone formation marker test should be carried out and the increased value should be observed. Intervals between the 2

assessments are: a) before starting drug and b) after starting drug for at least 3 months. Change of BTMs should be more than 30–40% [133] to interpret an actual change. As measurements of BTMs have high variation and less convenience (NPO for 12 h before morning blood collection for each follow-up), it is not widely used.

8.2. Assessment of correctness and compliance of drug use

Correctness, compliancy or incompliancy and persistency of drug use should be assessed. Problems usually relate to oral medication. Assessments can be performed by inquiring about correctness and persistence of drug use from patients in each visit. Checking to see whether patients prepare their own medication or have it done for them is essential to the assessment. Physical examination of empty drug receptacles can also be useful to check for compliancy. The acceptable rate is 80% in a 1-year period (medication possession ratio: MPR $\geq 80\%$) [134].

9. Period of treatment

There is still no conclusion regarding the exact period of treatment. Treatment duration depends on various factors including difference of medications, personal patient factors, results from clinical trials, etc. In general, continual use of medication is recommended until there is a satisfied reduction of risks for fracture in each individual. The indefinite treatment period may result in many problems including financial burden since it is not possible to reduce the risk of fracture to zero and because there is no data on long term efficacy. A clinical placebo comparative study in human

Table 3
Guideline for self-care for patients receiving glucocorticoids.

1. Supplementation of elemental calcium 1200 mg/day
2. Receiving at least 800 IU mg of vitamin D per day
3. Weight bearing exercise
4. No smoking
5. Limited alcoholic drinking to less than 3 units/day
6. Learn and practice methods for fall prevention
7. The physician in charge must perform a reassessment for the dosage of glucocorticoid to achieve the lowest dosage for disease control.
Immunosuppressive drugs should be considered for dosage reduction. Oral glucocorticoid or changing from oral drug to skin paste or respiratory tract application spray form

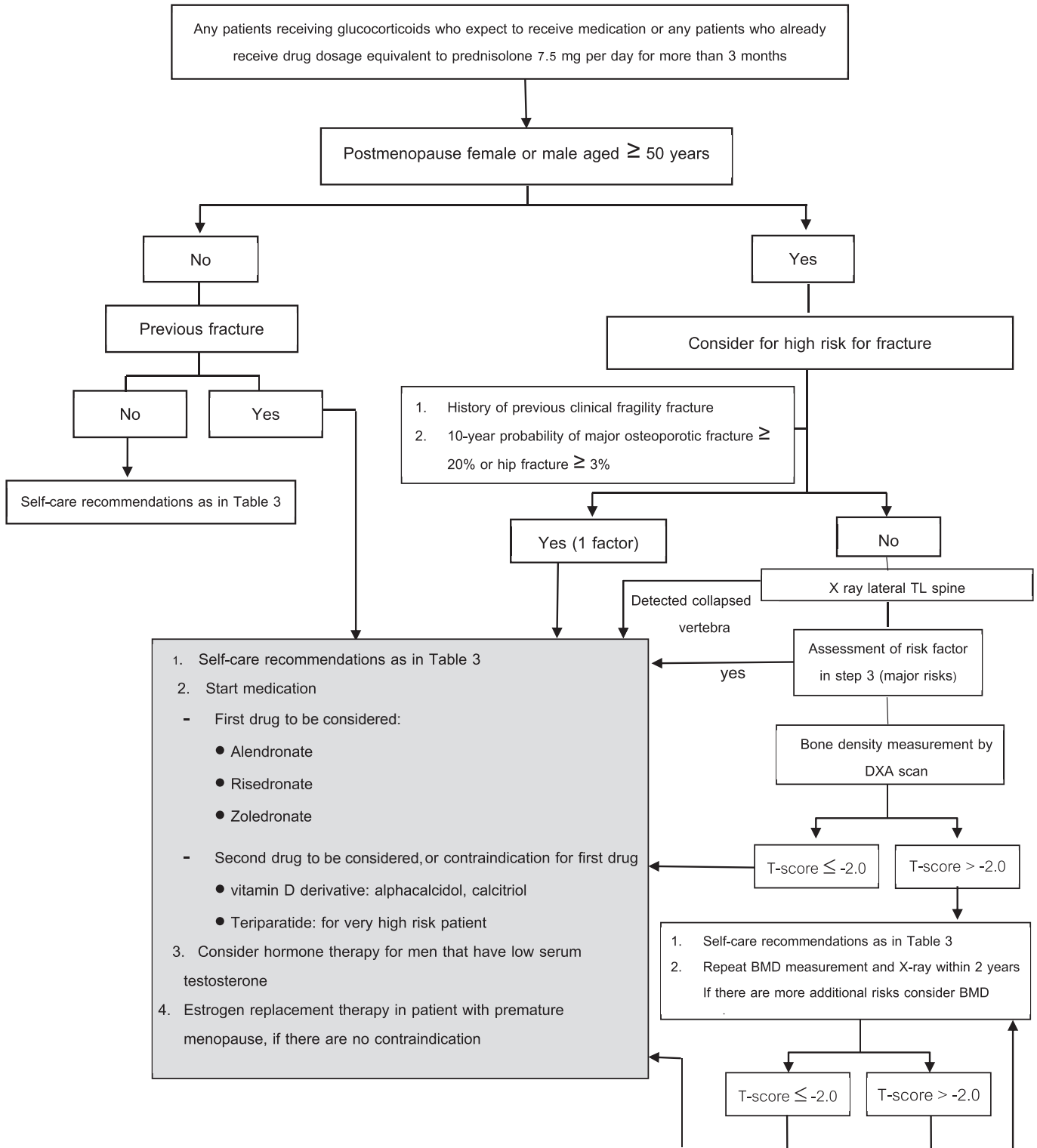


Fig. 1. Algorithm for treatment of glucocorticoid-induced osteoporosis.

subject to assess anti-fracture efficacy is usually limited to less than a 5 years period due to ethical constraints in human experiment. It is also worth noting that there is a return of fracture risk after drug cessation. Therefore, in general practice, if there are no serious long-term adverse events, continuous drug use is suggested.

As for the bisphosphonates group of drugs, long-term adverse events such as osteonecrosis of the jaw and atypical femoral fracture have been reported as a result of drug accumulation in bone. A drug cessation or “drug holiday” [135] can be considered at 3–5 years if there is good compliance and persistence, no previous vertebral fracture, hip fracture or

other non-vertebral fracture, no new fracture after medication and BMD by axial DXA results shows significant increase bone density (femoral neck BMD more than -2.5 S.D).

10. Guideline for treatment of osteoporosis due to glucocorticoids use

10.1. Treatment of osteoporosis due to glucocorticoid use by medication

Treatment of osteoporosis starts with non-medication treatment. In patients who receive glucocorticoid, the recommendation for self-care (described in Table 3) should be given [136] and glucocorticoid dosage reassessment is needed to achieve the lowest possible dosage for disease control. Immunosuppressive drugs should be considered for dosage reduction. Oral glucocorticoid or form change of oral drug to that of skin paste or respiratory tract application spray form have fewer adverse effects on bone.

Patients receiving glucocorticoids who expect to receive medication or patients who currently receive 7.5 mg of prednisolone per day for more than 3 months [137,138] should be evaluated for risk factors of fracture. A factor that is present it is an indication for treatment of osteoporosis as shown in Fig. 1.

10.2. Indication for pharmacological treatment of glucocorticoid-induced osteoporosis

10.2.1. Assessment of risk factors in step 1

1. In menopausal women or men aged over 50 years with history of clinical fragility fracture and/or having 10-year probability of hip fracture $\geq 3\%$ [136,139] by calculation using FRAX™ adjusted 10-year probability of major osteoporotic fracture and hip fracture based on the daily dosage of glucocorticoids [139] as shown in Table 4.
2. In premenopausal women or men aged less than 50 years, medication is indicated if there is a history of previous fracture [136]. There is a precaution in using bisphosphonates in childbearing-aged women. Contraception is recommended during bisphosphonates treatment. It is necessary to properly inform the patient prior to starting the drug since bisphosphonates can accumulate in bone

Table 4
Risk adjustment for fracture in 10 years due to glucocorticoids based on age and daily dosage of glucocorticoids (Quoted and modified from [139]).

Dosage	Drug dosage equivalent to prednisolone (mg/day)	Factor for multiplication to adjust the risk (from risk value in FRAX)
% Risk for hip fracture		
Low	<2.5	0.65
Medium	2.5–7.5	Adjustment is not required
High	>7.5	1.20
% Risk for major osteoporotic fracture		
Low	<2.5	0.80
Medium	2.5–7.5	Adjustment is not required
High	>7.5	1.15

and can pass through the placenta and accumulate in bone of fetus in utero [140].

10.2.2. Assessment of risk factors in step 2

Thoraco-lumbar spine X-ray

3. Evidence of collapsed vertebra from X-ray [141].

10.2.3. Assessment of risk factors in step 3

4. Findings for other major risks. If there are 2 or more factors
 - 4.1 Body mass index ≤ 20 kg/m² [26]
 - 4.2 Paternal or maternal history of hip fracture [25].
 - 4.3 Receiving more than 20 mg glucocorticoids for 3 months [142].
 - 4.4 Rheumatoid arthritis [143].

10.2.4. Assessment of risk factors in step 4

Examination of bone density

5. Axial DXA shows T-score less than -2.0 at spine or hip [144].

Conflict of interest

All authors have no conflict of interest..

References

- [1] Mahidol Population Gazette. Institute of Population and Social Research. Mahidol University; 2008.
- [2] Mahidol Population Gazette. Institute of Population and Social Research. Mahidol University; 2015.
- [3] Taechakraichana N, Angkawanich P, Panyakhamlerd K, Limpaphayom K. Postmenopausal osteoporosis: what is the real magnitude of problem? J Med Assoc Thai 1998;81:397–401.
- [4] Limpaphayom K, Taechakraichana N, Jaisamrarn U, Bunyavejchevin S, Chaikittisilpa S, Poshyachinda M, et al. Prevalence of osteopenia and osteoporosis in Thai women. Menopause 2001;8:65–9.
- [5] Phadungkiat S, Chariyalertsak S, Rajatanavin R, Chiengthong K, Suriyawongpaisal P, Woratanarat P. Incidence of hip fracture in Chiang Mai. J Med Assoc Thai 2002;85:565–71.
- [6] Wongtriratanachai P, Luevitonvechkij S, Songpatanasilp T, Sribunditkul S, Leerapun T, Phadungkiat S, et al. Increasing incidence of hip fracture in Chiang Mai. Thai J Clin Densitom 2013;16(3): 347–52.
- [7] Nevitt MC, Ettinger B, Black DM, Stone K, Jamal SA, Ensrud K, et al. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med 1998;128: 793–800.
- [8] Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR, for the Study of Osteoporotic Fractures Research Group. Vertebral fractures and mortality in older women; a prospective study. Arch Intern Med 1999;159:1215–20.
- [9] Pongchaiyakul C, Nguyen ND, Jones G, Center JR, Eisman JA, Nguyen TV. Asymptomatic vertebral deformity as a major risk factor for subsequent fractures and mortality: a long-term prospective study. J Bone Miner Res 2005;20(8):1349–55.
- [10] Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 1999;353:878–82.

- [11] Scaf-Klomp W, van Sonderen E, Sanderman R, Ormel J, Kempen GI. Recovery of physical function after limb injuries in independent older people living at home. *Aging* 2001;30:213–9.
- [12] Vaseenon T, Luevitoonvechkij S, Wongtriratanachai P, Rojanasthien S. Long-term mortality after osteoporotic hip fracture in Chiang Mai. *Thail J Clin Densitom* 2010;13:63–7.
- [13] Lewsirirat S, Thanomsingh P. Mortality and ambulatory status after intertrochanteric fracture treated at Maharat Nakhon Ratchasima Hospital, Thailand. *Thai J Orthop Surg* 2010;34(3–4):5–12. <http://thailand.digitaljournals.org/index.php/JRCOST/article/view/4555>.
- [14] Chaysri R, Leerapun T, Klunklin K, Chiewchantanakit S, Luevitoonvechkij S, Rojanasthien S. Factors related to mortality after osteoporotic hip fracture treatment at Chiang Mai University Hospital, Thailand, during 2006 and 2007. *J Med Assoc Thai* 2015; 98(1):59–64.
- [15] Koh LK, Sedrine WB, Torralba TP, Kung A, Fujiwara S, Chan SP, et al. A simple tool to identify Asian women at increased risk of osteoporosis. *Osteoporos Int* 2001;12:699–705.
- [16] Pongchaiyakul C, Nguyen ND, Pongchaiyakul C, Nguyen TV. Development and validation of a new clinical risk index for prediction of osteoporosis in Thai women. *J Med Assoc Thai* 2004;87:910–6.
- [17] FRAX-WHO fracture risk assessment tool, <http://www.shef.ac.th/FRAX/tool.jsp>.
- [18] Pongchaiyakul C, Leerapun T, Wongsiri S, Songpatanasilp T, Taechakraichana N. Value and validation of RCOST and TOPF clinical practice guideline for osteoporosis treatment. *J Med Assoc Thai* 2012; 95(12):1528–35.
- [19] NOF(National Osteoporosis Foundation). Clinician guide for prevention and treatment of osteoporosis. 2008. http://osteoporosis.utorontoeit.com/PDFs/NOF_Clinicians_Guide.pdf.
- [20] Gallagher JC. The pathogenesis of osteoporosis. *Bone Miner* 1990;9(3): 215–27.
- [21] National Osteoporosis Foundation. Osteoporosis: review of the evidence for prevention, diagnosis, and treatment and cost-effectiveness analysis. *Osteoporos Int* 1998;8(Suppl 4):S1–80.
- [22] World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. No. 843 of Technical Reports Series. Geneva World Health Organ Tech Rep Ser. 1994;843:1–129.
- [23] Bennett HS, Dienstfrey A, Hudson LT, Oreskovic T, Fuerst T, Shepherd J. Standards and measurements for assessing bone health-workshop report co-sponsored by the International Society for Clinical Densitometry (ISCD) and the National Institute of Standards and Technology (NIST). *J Clin Densitom* 2006;9:399–405.
- [24] Khan AA, Hodsman AB, Papaioannou A, Kendler D, Brown JP, Olszynski WP. Management of osteoporosis in men: an update and case example. *CMAJ* 2007;176:345–8.
- [25] Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Eisman JA, et al. A family history of fracture and fracture risk: a meta-analysis. *Bone* 2004;35(5):1029–37.
- [26] De Laet C, Kanis JA, Oden A, Johanson H, Johnell O, Delmas P, et al. Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporos Int J Establ Result Coop Between Eur Found Osteoporos Natl Osteoporos Found U S A* 2005;16(11):1330–8.
- [27] Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. *J Clin Densitom* 2013 Oct-Dec;16(4):455–66.
- [28] Juozaityte E, Aleknavicius E, Janciauskiene R, Cesas A, Pipiriene-Zelviene T, Liutkauskiene S, et al. Guidelines for diagnostics and treatment of aromatase inhibitor-induced bone loss in women with breast cancer: a consensus of Lithuanian medical oncologists, radiation oncologists, endocrinologists, and family medicine physicians. *Med Kaunas* 2014;50(4):197–203.
- [29] Wang A, Obertová Z, Brown C, Karunasinghe N, Bishop K, Ferguson L, et al. Risk of fracture in men with prostate cancer on androgen deprivation therapy: a population-based cohort study in New Zealand. *BMC Cancer* 2015;15:837.
- [30] Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, et al. A meta-analysis of previous fracture and subsequent fracture risk. *Bone* 2004 Aug;35(2):375–82.
- [31] National Osteoporosis Guideline Group (NOGG). Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. March 2014.
- [32] Pongchaiyakul C, Panichkul S, Songpatanasilp T, Nguyen TV. A nomogram for predicting osteoporosis risk based on age, weight and quantitative ultrasound measurement. *Osteoporos Int* 2007;18(4):525–31.
- [33] Seibel MJ. Biochemical markers of bone turnover: part I: biochemistry and variability. *Clin Biochem Rev* 2005;26:97–122.
- [34] Gerdhem P, Ivaska KK, Alatalo SL, Halleen JM, Hellman J, Isaksson A, et al. Biochemical markers of bone metabolism and prediction of fracture in elderly women. *J Bone Miner Res* 2004;19:386–93.
- [35] Riis BJ, Hansen MA, Jensen AM, Overgaard K, Christiansen C. Low bone mass and fast rate of bone loss at menopause: equal risk factors for future fracture: a 15-year follow-up study. *Bone* 1996;19:9–12.
- [36] Riggs B, Melton LJ, O'Fallon WM. Drug therapy for vertebral fractures in osteoporosis: evidence that decreases in bone turnover and increases in bone mass both determine antifracture efficacy. *Bone* 1996;18:S197–201.
- [37] Szulc P, Delmas P. Biochemical markers of bone turnover in osteoporosis. In: Marcus R, Feldman D, Nelson DA, Rosen CJ, editors. *Osteoporosis*. 3rd ed. San Diego: Elsevier Academic Press; 2008. p. 1519–45.
- [38] Nugaram R, Atmaca A, Kleerekoper M. Evaluation of the patient with osteoporosis or at risk for osteoporosis. In: Marcus R, Feldman D, Nelson DA, Rosen CJ, editors. *Osteoporosis*. 3rd ed. San Diego: Elsevier Academic Press; 2008. p. 1437–47.
- [39] De Villiers TJ, Gass MLS, Haines CJ, Hall JE, Lobo RA, Pierroz DD, et al. Global consensus statement on menopausal hormone therapy. *Climacteric* 2013;16:203–4.
- [40] Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;288:321–33.
- [41] Tremollieres FA, Pouilles JM, Ribot C. Withdrawal of hormone replacement therapy is associated with significant vertebral bone loss in postmenopausal women. *Osteoporos Int* 2001;12:385–901.
- [42] <http://www.nlm.nih.gov/medlineplus/magazine/issues/winter11/articles/winter11pg12.html>.
- [43] Bonjour JP. Protein intake and bone health. *Int J Vitam Nutr Res* 2011; 81:134–42.
- [44] Kerstetter JE, O'Brien KO, Insogna KL. Dietary protein, calcium metabolism, and skeletal homeostasis revisited. *Am J Clin Nutr* 2003; 78:584S–92S.
- [45] Dawson-Hughes B, Harris SS. Calcium intake influences the association of protein intake with rates of bone loss in elderly men and women. *Am J Clin Nutr* 2002;75:773–9.
- [46] Soontrapa S, Soontrapa S, Bunyaratavej N. Serum concentration of undercarboxylated osteocalcin and the risk of osteoporosis in Thai elderly women. *J Med Assoc Thai* 2005;88(Suppl 5):S29–32.
- [47] Howe TE, Shea B, Dawson LJ, Downie F, Murray A, Ross C, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev* 2011 Jul 6;(7):CD000333. <http://dx.doi.org/10.1002/14651858.CD000333>.
- [48] Martyn-St James M, Carroll S. A meta-analysis of impact exercise on postmenopausal bone loss: the case for mixed loading exercise programmes. *Br J Sports Med* 2009;43:898–908.
- [49] Gomez-Cabello A, Ara I, Gonzalez-Aguero A, Casajús JA, Vicente-Rodríguez G. Effects of training on bone mass in older adults: a systematic review. *Sports Med* 2012;42:301–25.
- [50] Martyn-St James M, Carroll S. Meta-analysis of walking for preservation of bone mineral density in postmenopausal women. *Bone* 2008;43:521–31.
- [51] Kemmler W, Lauber D, Weineck J, Hensen J, Kalender W, Engelke K. Benefits of 2 years of intense exercise on bone density, physical fitness, and blood lipids in early postmenopausal osteopenic women. *Arch Intern Med* 2004;164:1084–91.
- [52] Brunton S, Carmichael B, Gold D, et al. Osteoporosis. In: Kauffman TL, Moran ML, editors. *Geriatric rehabilitation manual*. 2nd ed. Toronto: Churchill Livingstone-Elsevier; 2007. p. 121–45.

- [53] Sinaki M, Itoi E, Wahner HW, Wollan P, Gelzcer R, Mullan BP, et al. Stronger back muscles reduce the incidence of vertebral fractures: a prospective 10 year follow-up of postmenopausal women. *Bone* 2002; 30:836–41.
- [54] Campbell AJ, Robertson MC, Gardner MM, Norton RN, Tilyard MW, Buchner DM. Randomized controlled trial of a general practice programme of home based exercise to prevent falls in elderly women. *Br Med J* 1997;315:1065–9.
- [55] Senator John Glenn. Exercise: a guide from the National Institute of Aging. NIH Publication No. 01–4258; April 2004. Available access from, <http://www.nih.gov/niia>.
- [56] Wolf SL, Barnhart HX, Kutner NG, McNeely E, Coogler C, Xu T. Reducing frailty and falls in older persons: an investigation of Tai Chi and computerized balance training. *J Am Geriatr Soc* 1996;44:489–97.
- [57] Sinaki M. Osteoporosis. In: Braddom RL, editor. *Physical medicine and rehabilitation*. 4th ed. Philadelphia: Elsevier; 2011. p. 913–33.
- [58] Carter ND, Khan KM, McKay HA, Petit MA, Waterman C, Heinonen A, et al. Community-based exercise program reduces risk factors for falls in 65- to 75-year-old women with osteoporosis: randomized controlled trial. *CMAJ* 2002;167:997–1004.
- [59] Buckwalter JA, Glimcher MJ, Cooper RR. Bone biology. Part II: formation, form, modeling, remodeling, and regulation of cell function. *J Bone Jt Surg* 1995;77:1276–89.
- [60] Kelly GA. Exercise and regional bone mineral density in postmenopausal women: a meta-analytic review of randomized trials. *Am J Phys Med Rehabil* 1998;77:76–87.
- [61] American Geriatrics Society, British Geriatrics Society, American Academy of Orthopaedic Surgeons Panel on Falls Prevention. Guideline for the prevention of falls in older persons. *J Am Geriatr Soc* 2001;49: 664–72.
- [62] Tinetti ME. Preventing falls in elderly persons. *N Engl J Med* 2003;348: 42–9.
- [63] Chang JT, Morton SC, Rubenstein LZ, Mojica WA, Maglione M, Suttrop MJ, et al. Interventions for the prevention of falls in older adults: systematic review and meta-analysis of randomized clinical trials. *BMJ* 2004;328:680–6.
- [64] Dawson-Hughes B, Fuleihan GEH, Clark P. Bone care for the postmenopausal woman. *IOF* 2013;11.
- [65] Rubenstein LZ, Josephson KR, Robbins AS. Falls in the nursing home. *Ann Intern Med* 1994;121:442–51.
- [66] Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med* 1988;319: 1701–7.
- [67] Nevitt MC, Cummings SR, Kidd S, Black D. Risk factors for recurrent non-syncopal falls: a prospective study. *JAMA* 1989;261:2663–8.
- [68] Robbins AS, Rubenstein LZ, Josephson KR, Schulman BL, Osterweil D, Fine G. Predictors of falls among elderly people. Results of two population-based studies. *Arch Intern Med* 1989;149:1628–33.
- [69] Hendrich AL, Bender PS, Nyhuis A. Validation of the Hendrich II Fall Risk Model: a large concurrent case/control study of hospitalized patients. *Appl Nurs Res* 2003;16:9–21.
- [70] O'Connell B, Myers H. The sensitivity and specificity of the Morse Fall Scale in an acute care setting. *J Clin Nurs* 2002;11:134–6.
- [71] Nandy S, Parsons S, Cryer C, Underwood M, Rashbrook E, Carter Y, et al. Development and preliminary examination of the predictive validity of the Falls Risk Assessment Tool (FRAT) for use in primary care. *J Public Health (Oxf)* 2004;26:138–43.
- [72] El Miedany Y, Gardiner A, El Gaafary M, Toth M. Falls risk assessment score (FRAS): time to rethink. *J Clin Gerontol Geriatr* 2011;2:21–6.
- [73] Renfro MO, Fehrer S. Multifactorial screening for fall risk in community-dwelling older adults in the primary care office: development of the fall risk assessment & screening tool. *J Geriatr Phys Ther* 2011;34:174–83.
- [74] Podsiadlo D, Richardson S. The timed “Up & Go”: a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39:142–8.
- [75] Kuptniratsaikul V, Dejpratham P, Praditsuwan R. The timed up & go: the practical basic mobility skills assessment. *Siriraj Hosp Gaz* 2006;58: 588–91.
- [76] Mong Y, Teo TW, Ng SS. 5-repetition sit-to-stand test in subjects with chronic stroke: reliability and validity. *Arch Phys Med Rehabil* 2010;91: 407–13.
- [77] Weiner DK, Duncan PW, Chandler J, Studenski SA. Functional reach: a marker of physical frailty. *J Am Geriatr Soc* 1992;40:203–7.
- [78] Vellas BJ, Rubenstein LZ, Ousset PJ, Faisant C, Kostek V, Nourhashemi F, et al. One-leg standing balance and functional status in a population of 512 community-living elderly persons. *Aging (Milano)* 1997;9:95–8.
- [79] Costa-Dias MJ, Oliveira AS, Martins T, Araújo F, Santos AS, Moreira CN, et al. Medication fall risk in old hospitalized patients: a retrospective study. *Nurse Educ Today* 2014;34:171–6.
- [80] Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med* 2009;169:1952–60.
- [81] Mulrow CD, Gerety MB, Kanten D, Cornell JE, DeNino LA, Chiodo L, et al. A randomized trial of physical rehabilitation for very frail nursing home residents. *JAMA* 1994;271:519–24.
- [82] Lord SR, Dayhew J. Visual risk factors for falls in older people. *J Am Geriatr Soc* 2001;49:508–15.
- [83] Gillespie WJ, Gillespie LD, Parker MJ. Hip protectors for preventing hip fractures in older people. *Cochrane Database Syst Rev* 2010;6(10). CD001255.
- [84] Dawson-Hughes B. Serum 25-hydroxyvitamin D and muscle atrophy in the elderly. *Proc Nutr Soc* 2012;71:46–9.
- [85] Murad MH, Elamin KB, Abu Elnour NO, Elamin MB, Alkatib AA, Fatourechi MM, et al. Clinical review: the effect of vitamin D on falls: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011;96: 2997–3006.
- [86] Black DM, Cummings SR, Karf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996;348: 1535–41.
- [87] Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures. *JAMA* 1998;280:2077–82.
- [88] Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and non-vertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial: vertebral efficacy with risedronate therapy (VERT) study group. *JAMA* 1999;282:1344–52.
- [89] Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis: vertebral efficacy with risedronate therapy (VERT) study group. *Osteoporos Int* 2000;11:83–91.
- [90] McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2001;344:333–40.
- [91] Rizzoli R, Greenspan SL, Bone 3rd G, Schnitzer TJ, Watts NB, Adami S, et al. Two-year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis. *J Bone Miner Res* 2002;17:1988–96.
- [92] Harris ST, Watts NB, Li Z, Chines AA, Hanley DA, Brown JP. Two-year efficacy and tolerability of risedronate once a week for the treatment of women with postmenopausal osteoporosis. *Curr Med Res Opin* 2004;20:757–64.
- [93] Ralston SH, Binkley N, Boonen S, Kiel DP, Reginster JY, Roux C, et al. FOCUS-D trial group. Randomized trial of alendronate plus vitamin D3 versus standard care in osteoporotic postmenopausal women with vitamin D insufficiency. *Calcif Tissue Int* 2011;88(6): 485–94.
- [94] Kim KJ, Min YK, Koh JM, Chung YS, Kim KM, Byun DW, et al., VALUE study group. Efficacy and safety of weekly alendronate plus vitamin D₃ 5600 IU versus weekly alendronate alone in Korean osteoporotic women: 16-week randomized trial. *Yonsei Med J* 2014;55(3): 715–24.

- [95] Chesnut III CH, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004;19:1241–9.
- [96] Reginster JY, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2-year results from the MOBILE study. *Ann Rheum Dis* 2006;65:654–61.
- [97] Eisman JA, Civitelli R, Adami S, Czerwinski E, Recknor C, Prince R, et al. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. *J Rheumatol* 2008;35:488–97.
- [98] Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809–22.
- [99] Colon-Emeric CS, Caminis J, Suh TT, Pieper CF, Janning C, Magaziner J, et al. The HORIZON recurrent fracture trial: design of a clinical trial in the prevention of subsequent fractures after low trauma hip fracture repair. *Curr Med Res Opin* 2004;20:903–10.
- [100] Lyles KW, Colon-Emeric CS, Magaziner J, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007;357:1799–809.
- [101] Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al., American Society for Bone and Mineral Research. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2007;22:1479–91.
- [102] Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for bone and mineral Research. *J Bone Miner Res* 2014;29:1–23.
- [103] Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis (SOTI study). *N Engl J Med* 2004;350:459–68.
- [104] Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of Peripheral Osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005;90:2816–22.
- [105] European Medicine Agency (EMA) Report. Protelos/Osseora to remain available but with further restrictions. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Protelos_and_Osseora/European_Commission_final_decision/WC500173034.pdf.
- [106] Cummings SR, Martin JS, McClung MR, Siris ES, Eastell R, Reid IR, et al., for the FREEDOM trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756–65.
- [107] McClung MR, Lewiecki EM, Geller ML, Bolognese MA, Peacock M, Weinstein RL, et al. Effect of denosumab on bone mineral density and biochemical markers of bone turnover: 8-year results of phase-2 clinical trial. *Osteoporos Int* 2013;24:227–35.
- [108] Etinger B, Black DM, Cumming S, Knickerbocker RK, Nickelsen T, Genant HK, et al., the MORE study group. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-years randomized clinical trial. *JAMA* 1999;282:637–45.
- [109] Martino S, Cauley JA, Barrett-Connor E, Powles TJ, Mershon J, Disch D, et al., for the CORE Investigators. Invasive breast cancer risk reduction in postmenopausal women with osteoporosis treated with raloxifene for 8 years: results from the Continuing Outcomes Relevant to Evista (CORE) trial. *J Natl Cancer Inst* 2004;96:1751–61.
- [110] Shiraki M, Shiraki Y, Aoki C, Miura M. Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. *J Bone Miner Res* 2000;15:515–21.
- [111] Cockayne S, Adamson J, Lanham-New S, Shearer MJ, Gilbody S, Torgerson DJ. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med* 2006;166:1256–61.
- [112] Inoue T, Fujita T, Kishimoto H, Makino T, Nakamura T, Nakamura T, et al. Randomized controlled study on the prevention of osteoporotic fractures (OF study): a phase-IV clinical study of 15 mg menatetrenone capsules. *J Bone Miner Metab* 2009;27:66–75.
- [113] Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434–41.
- [114] Nevitt MC, Chen P, Dore RK, Reginster JY, Kiel DP, Zanchetta JR, et al. Reduced risk of back pain following teriparatide treatment: a meta-analysis. *Osteoporos Int* 2006;17(2):273–80.
- [115] Diez-Perez A, Gonzalez-Macias J. Inadequate responders to osteoporosis treatment: proposal for an operational definition. *Osteoporos Int* 2008;19:1511–6.
- [116] Lewiecki EM, Watts NB. Assessing response to osteoporosis therapy. *Osteoporos Int* 2008;19:1363–8.
- [117] Sloan AV, Martin JR, Li S, Li J. Parathyroid hormone and bisphosphonate have opposite effects on stress fracture repair. *Bone* 2010;47:235–40.
- [118] Alkhiary YM, Gerstenfeld LC, Krall E, Westmore M, Sato M, Mitlak BH, et al. Enhancement of experimental fracture-healing by systemic administration of recombinant human parathyroid hormone (PTH 1-34). *J Bone Jt Surg Am* 2005;87:731–41.
- [119] Rubery PT, Bukata SV. Teriparatide may accelerate healing in delayed union of Type III odontoid fractures: a report of 3 cases. *J Spinal Disord Tech* 2010;23:151–5.
- [120] Chintamaneni S, Finzel K, Gruber BL. Successful treatment of sternal fracture nonunion with teriparatide. *Osteoporos Int* 2010;21:1059–63.
- [121] Gomberg SJ, Wustrack RL, Napoli N, Arnaud CD, Black DM. Teriparatide, vitamin D, and calcium healed bilateral subtrochanteric stress fractures in a postmenopausal woman with a 13-year history of continuous alendronate therapy. *J Clin Endocrinol Metab* 2011;96:1627–32.
- [122] Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3- year intervention study. *J Bone Miner Res* 2004;19(3):370–8.
- [123] Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int* 2014;25:2359–81.
- [124] Institute of Medicine (US) Committee to review dietary reference intakes for vitamin D and calcium. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Dietary reference intakes for calcium and vitamin D. Washington (DC): National Academies Press (US); 2011. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK56070/>. Access January 2015.
- [125] Moyer VA, U.S. Preventive Services Task Force. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2013;158(9):691–6.
- [126] Joint FAO/WHO Expert Consultation Panel. Preliminary report on recommended nutrient intakes. 1998.
- [127] Wallace AM, Gibson S, de la Hunt A, Lamberg-Allardt C, Ashwell M. Measurement of 25-hydroxyvitamin D in the clinical laboratory: current procedures, performance characteristics and limitations. *Steroids* 2010;75:477–88.
- [128] Vogeser M, Kyriatsoulis A, Huber E, Kobold U. Candidate reference method for the quantification of circulating 25-hydroxyvitamin D3 by liquid chromatography-tandem mass spectrometry. *Clin Chem* 2004;50:1415–7.
- [129] Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Washington, DC: National Academies Press; 2011.
- [130] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;96:1911–30.

- [131] Evaluation, treatment, and prevention of vitamin D Deficiency: an endocrine Society Clinical practice Guideline. *J Clin Endocrinol Metab* 2011;96:1911–30.
- [132] Thai Endocrine Society. Clinical guideline for vitamin D deficiency in Thailand. 2012.
- [133] Terreni A, Pezzati P. Biochemical markers in the follow-up of the osteoporotic patients. *Clin Cases Miner Bone Metab* 2012;9(2): 80–4.
- [134] Sampalis JS, Adachi JD, Rampakakis E, Vaillancourt J, Karellis A, Kindundu C. Long-term impact of adherence to oral bisphosphonates on osteoporotic fracture incidence. *J Bone Miner Res* 2012;27(1):202–10.
- [135] Diab DL, Watts NB. Bisphosphonate drug holiday: who, when and how long. *Ther Adv Musculoskel Dis* 2013;5(3):107–11.
- [136] Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res* 2010;62(11):1515–26.
- [137] Hoes JN, Jacobs JW, Boers M, Boumpas D, Buttgerit F, Caeyers N, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2007;66(12):1560–7.
- [138] Geusens PP, de Nijs RN, Lems WF, Laan RF, Struijs A, van Staa TP, et al. Prevention of glucocorticoid osteoporosis: a consensus document of the Dutch Society for Rheumatology. *Ann Rheum Dis* 2004;63(3): 324–5.
- [139] Lekamwasam S, Adachi JD, Agnusdei D, Bilezikian J, Boonen S, Borgstrom F, et al. A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. *Osteoporos Int* 2012;23(9):2257–76.
- [140] Patlas N, Golomb G, Yaffe P, Pinto T, Breuer E, Ornoy A. Trans-placental effects of bisphosphonates on fetal skeletal ossification and mineralization in rats. *Teratology* 1999;60(2):68–73.
- [141] Siris ES, Genant HK, Laster AJ, Chen P, Misurski DA, Krege JH. Enhanced prediction of fracture risk combining vertebral fracture status and BMD. *Osteoporos Int* 2007;18(6):761–70.
- [142] van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatol Oxf* 2000;39(12):1383–9.
- [143] Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis register. *Arthritis Rheum* 2000;43(3):522–30.
- [144] Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. *Arthritis Rheum* 2003;48(11): 3224–9.