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I Definition, epidemiology, burden and etiology of osteoporosis

I-1 Definition and concept

In 2000, the National Institute of Health (NIH) of the United States (1) defined “osteoporosis” as a disease of deteriorating bone strength that leads to increasing risks for bone fracture. “Bone strength” by NIH’s definition composed of two major indexes which are bone density and bone quality.

I-2 Epidemiology of osteoporosis and osteoporotic fractures

2.1 Worldwide epidemiology

A report from WHO Consensus Development Conference in 2000 (2) described that in the United States there are approximately 1.3 million patients suffering from osteoporotic fractures per year. Among these, about 50% had vertebral fractures, another 25% had hip fractures and the last 25% had wrist fractures or others. Additionally, there were reports stating that about 30% of European women who were 50 years old or more had osteoporosis.

According to the United States National Health and Nutrition Survey (NHANES III) in 1997, there was an estimate that 13-18% of female American Caucasian having osteoporosis while 27-50% of all American Caucasian women had osteopenia, which enhanced the rate of onset for osteoporosis in these women when they become older. On the other hand, looking only at the American Caucasian female population aged 80 or more, about 70% of them will have osteoporosis.

In general, bone fractures are much more prevalent in men than in women since from adolescence to middle age men’s lifestyle and activities are generally more physically intense, including some activities that are more risky and/or more dangerous than those that are common to women. It was found that men experienced bone fracture as the consequences of high-energy trauma. However, after the age of 40-50 bone fracture incidence seems to be totally opposite to what occurs with females. Bone fractures from various parts of the body such as wrists, vertebra, pelvis and hip in women are substantially increased. (4) In these case fractures are the results of low-energy trauma; in other words, they are osteoporotic fractures. In the United States, there are about 500,000 cases of spinal fractures per year (4) and there are ten times more prevalent in women than in men. It can be said that half of American Caucasian females age of 70 or more have fractures at one or more vertebrae. (4) For hip fractures, the incidence rate in the Caucasian female population ranged from the highest, 737 fractures per 100,000 population per year for Norwegian females, to the lowest, of 280 fractures per 100,000 population for Finnish women. (5)
2.2 Epidemiology in Asia and Thailand

From the most recent information, the life expectancy of Thais is 69.5 years for men and 76.3 years for women. A survey in female patients from several public hospitals and from random examinations of women from all geographical parts of Thailand in 1998 and 2001 found that approximately 19-21% of women age 40 or more have lumbar spine osteoporosis and 11-13% have femoral neck osteoporosis. In addition this survey followed the guidelines for osteoporosis diagnosis from the WHO which specifies osteoporosis is present when the T-score is at least minus 2.5 SD (standard deviation) of the average BMD value for a young healthy population.

In Thailand, there is a study carried out in Chiang Mai between 1997 and 1998 described that the incidence of hip fractures in both males and females age 50 or more was 162 fractures per 100,000 population. In the population age of 75 or more, the incidence of hip fractures rose to 851 per 100,000 population. Among these, if limited to women age 50 or more, the incidence of hip fractures increased to 269 fractures per 100,000 population and this number will rise to 1,011 fractures per 100,000 population when the age limit is increased to 75 or more. These incidence rates are close to the incidence rates of hip fractures in other Asian countries. Also the incidence rates in Asian countries are increasing every year. For example, with Hong Kong Chinese females, the incidences for hip fracture almost doubled from 179 fractures per 100,000 population in 1965 to 389 fractures per 100,000 population in 1985. Recently in Japan, a study shows that the incidence of hip fractures rose from a total of 92,400 cases from 1997 to 2001 to 117,900 yearly. There is also an estimation of more than 6 million cases of hip fracture occurring worldwide in 2050 and half of these, or 3 million cases, will happen in Asia.

I-3 Burden and impact of osteoporosis and osteoporotic fractures

Generally, osteoporosis is a disease without symptoms but the clinical consequences of this disease are increased risks of having trauma from bone fractures which can be classified into two categories.

1. **Low-energy trauma** such as hip fractures caused by falling from a standing position or falling from a height which is close to the person’s height.
2. **Fractures without external compression** such as spinal fractures from bending or from lifting heavy objects.

All of these types of fractures are collectively called osteoporotic fractures, which are the result of the loss of bone strength. As a consequence, osteoporotic fractures can significantly cause the quality of life.
3.1 Osteoporosis related mortality and morbidity

1. Osteoporotic vertebral fractures usually occur during normal working activity or daily routine without any history of accidents. This may be the reason why 40% of women who have osteoporotic vertebral fractures fail to notice their symptoms.

2. Osteoporotic fractures can cause minor symptoms such as mild to heavy pain that require hospital admission. In contrast, the morbidity (12) and mortality (13) rate of patients with osteoporotic vertebral fracture is much higher than in patients with no history of bone fracture. These patients will have chronic back pain, height loss, kyphosis and/or scoliosis which can lead to flatulence and loss of appetite due to downsizing of the abdomen. Also, patients will experience some pain in the waist area since the ribs are bending toward the pelvis.

3. Patients might lose functional ability because of multiple fractured vertebrae. The more fractured vertebrae there are, the greater the increase in morbidity and mortality. (12-14) Also multiple vertebral fractures lead to increasing fragility for the rest of the vertebras and the hips. (14)

4. Hip fractures are the most serious fractures and they have highest mortality rate after the fracture occurred and lead to higher risks for disability and loss of competence for daily activities. Apart from that, the cost of care management for patients with hip fractures is much higher than for the other types of fractures because patients suffering from hip fracture must have surgery, otherwise they may never be able to walk again. Moreover, these patients are may be vulnerable to multiple post-surgery complications which sometimes can be fatal.

5. A study of elderly Caucasian patients who had hip fracture (15-16), showed an approximate 20% mortality rate within one year post-fracture. For the surviving patients, 30% had permanent disability and will need care-takers or have to live in a nursing community. Moreover, 40% of them will have to live with walking assistance devices and 80% will lose one of their daily habits.

6. In Thailand, a study in Chiang Mai (17) revealed the following mortality rate after having a hip fracture: 2.1% died during hospital recovery, 9%, 12% and 17% of cases died after 3, 6, 9 months post-fracture. The survey of quality of life after hip fracture in Thais found that one in every five patients (or 22%) cannot walk by themselves and 23% have to be on a wheelchair. In addition, these patients will need help with daily rituals such
as 11% need help bathing, 10% need help dressing, 22% need help defecating and 5% need help eating.

3.2 Health economic aspect of osteoporotic fractures

1. From the report of the International Osteoporosis Foundation (IOF) which surveyed the cost of treatment and care after osteoporotic fractures in Europe (19), 25 billion Euros were spent on health management of osteoporotic fractures. In Britain approximately 1.8 billion pounds were spent for osteoporotic fracture management (20). In the United States, the National Osteoporosis Foundation (NOF) estimated that in 2005, 17 billion dollars were used in osteoporotic fracture management (21).

2. In Thailand, a nation-wide assessment of this health issue has never been done but there is an estimate that the cost of treatment and care of one hip fracture patient would be around 120,000 baht per year (22).

I-4 Pathogenesis and etiology

4.1 Pathogenesis

1. Osteoporosis is caused by the reduction of bone mass and bone quality. The two main reasons of this phenomenon are less storage of bone mass and abnormally increased bone resorption. After birth, bone will acquire more mass by increased bone formation while bone resorption is less which results in deposition of bone tissue until the point when the bone stops growing and there will be the highest density of bone mass for that individual; this can be called “peak bone mass”. The peak bone mass in Thai population is at 30-34 years of age (8). After that, there is a balance between bone formation and bone resorption which results in constant bone mass. At the age of 40-45 years the rate of bone formation will start to decline and that equals to a balance shift towards bone resorption and results in decreasing bone mass. Then, after a woman enters menopause, the rate of bone resorption will increase tremendously the outcome of which is the continuous loss of bone mass. Then, eventually, bone mass will decline to the point where it will enhance the risk of bone fracture which is called the state of having “osteoporosis”. Therefore, any treatment or prevention that decelerates the rate of bone resorption will decrease the risk for having osteoporosis.

2. The most important factor for bone mass is ethnicity. It was found that the highest bone mass is Africans, followed by Caucasians and Asians. In terms of genetics, it was found that, the peak bone mass of a person is
closely related to his/her mother’s bone mass density \(^{(23-25)}\). On the other hand, strength training in children and adolescents will increase their peak bone mass \(^{(28, 29)}\). In contrast, cigarette smoking and consuming alcohol beverages will reduce the peak bone mass \(^{(30)}\)

3. The rate for bone resorption in women will be high and rapid during the first 10 years after menopause and this is called “postmenopausal bone loss”. The rate of bone mass decline can be about 3-5% per year which is the caused by the reduction of estrogen levels which induces osteoclast activity, thus increasing bone resorption. This event usually take place with cancellous or trabecular bone rather than with cortical bone, hence bone fracture in postmenopausal women often happens to more porous bone such as in the spine. After this period, the rate of bone deterioration will decline, being almost the same as what occurs in males \(^{(31)}\). However, some women may lose bone at a higher rate during the rest of their lives.

4. The rate of bone resorption in men is less than in women, only 1-2% per year, which starting from the age of 40-50. In both men and women the major reason for bone loss is from inefficient osteoblasts which can be called “age-related bone loss”

5. For both genders, there will be exponentially increased incidences for osteoporotic fracture as age increases. In women, the incidences increase from the age of 65 while in men the incidences start to rise during the age of 70-75. The rate of osteoporotic fracture incidence will increase as the age increases.

6. Other factors that accelerate the bone resorption are the use of glucocorticoids, vitamin D deficiency, some endocrine diseases such as thyroid and parathyroid diseases and rheumatoid arthritis.

7. The most important cause of osteoporotic fractures is external compression which usually occurs because of a fall. Factors in a fall commonly \(^{(32)}\) are postural reflex control, muscle coordination, visualization and fat padding around the bone that can help absorb the compression. One can see that the age is extremely relevant to all of these factors. Apart from the osteoporosis that happens with aging, other mechanisms for preventing from falling are also worsened, therefore the risks for bone fracture are increased.
Reference


II Diagnosis and bone mass assessment in osteoporosis

II-I History, physical examination and differential diagnosis

1.1 Classification of osteoporosis(1)

Osteoporosis is classified into:

Primary osteoporosis consisting of
1. Postmenopausal osteoporosis, mainly caused by a lack of estrogen hormones.
2. Age-related or senile osteoporosis, caused by a decrease in bone production resulting from the deterioration of osteoblast, occurred in both male and female.

Secondary osteoporosis showing in table 2.1

Table 2.1 Common causes of secondary osteoporosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Endocrine disease</td>
<td>Cushing’s syndrome, Hypogonadism, Hyperthyroidism, Hyperparathyroidism</td>
</tr>
<tr>
<td>2. Drugs</td>
<td>Glucocorticoids, Antiplatelets (Heparin, Warferin), Antiepilepsy (Phenytoin, Phenobarbital), Immunosuppressants</td>
</tr>
<tr>
<td>3. Medical disease</td>
<td>Renal failure, Chronic liver disease, Malabsorption syndromes or gastric surgery, Rheumatoid Arthritis</td>
</tr>
<tr>
<td>4. others</td>
<td>Nutrition deficiency, Cancer and multiple myeloma, Osteogenesis imperfecta</td>
</tr>
</tbody>
</table>
II-2 Risk factors for osteoporosis and osteoporotic fractures

2.1 Risk factors for osteoporosis and osteoporotic fracture

Without bone fracture, there may be no obvious physical evidence of osteoporosis during an examination, and a patient may not yet experience any symptoms. As a consideration of public health economics, it’s not reasonable to check everyone using a bone densitometer, so using risk assessment which is easy, comfortable and safe seems to be a more appropriate method.\(^{(2)}\)

Risk factors relating to osteoporosis and osteoporotic fracture in menopausal women

*Non-modifiable risk factors*

1. Age (65 years and older)
2. Female
3. Caucasian and Asian women
4. Early menopause (before age 45) and those whose ovaries were removed before menopause
5. Small body build
6. Father, mother or sister have osteoporosis or an osteoporotic fracture
7. Experience of bone fragility fracture

*Modifiable risk factors*

1. Inadequate calcium intake
2. Sedentary lifestyle
3. Regularly smoke
4. Regularly drink alcohol
5. Regularly drink excess coffee
6. Body mass index lower than 19 kilograms/square meter
7. Estrogen deficiency in pre-menopause: for example, taking gonadotropin releasing hormone (GnRH) analogue or excess exercise
8. Propensity for falling due to impaired vision

2.2 Risk assessment of osteoporotic fracture using WHO-FRAX™

According to studies in Europe, North America and Australia by the WHO,\(^{(3)}\) risk factors can be assessed by choosing only risk factors with the following characteristics.

1. Independent to BMD
2. Supported by several studies as an important risk factor
3. Can adjust age, gender and type of fractures
4. Easy to understand and use by a general practitioner
5. Can be reduced by drug treatment (only in case of modification risks)
This evaluation results in nine important risk factors as in table 2.2. These risk factors also include bone mass density (BMD) mainly using only femoral neck BMD, or using body mass index (BMI) in case BMD is not available to measure. These values using instead of risk factors are resulted in Yes/No. Using numeric values only for age and BMD/BMI.

Table 2.2 Important risk factors used in FRAX™ by the WHO

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>BMD (FN) / BMI (T-score or kg/M²)</td>
<td></td>
</tr>
<tr>
<td>A prior fragility fracture (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Parental history of hip fracture (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Current tobacco smoking (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Long-term use of oral glucocorticoids (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Other causes of secondary osteoporosis (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Daily alcohol consumption of three or more units daily (yes/no)</td>
<td></td>
</tr>
</tbody>
</table>

Note: BMD (FN) = femoral neck bone mass density, BMI = bone mass density
Source: the WHO task force conference held in Brussels, Belgium in May 2004

This information and risk factors are identified and estimated in a complete program calculated into a 10-year probability of fracture. This FRAX™ program can be accessed via the internet at http://www.shef.ac.uk/FRAX. In fact, this 10-year probability varies by country and race. On the website there are FRAX™ of many countries, including Japan and China as Asian countries and US-Asian resulting in a 10-year probability for hip fracture and a 10-year probability for other major osteoporotic fractures. Both values can be used to assess patient risk for therapeutic threshold, for example, currently in US, in case patient has not fracture or BMD in lower than 2.5, a 10-year probability of fracture will be calculated and it will determine weather drug treatment will be use — drug treatment can be used in case that patient has 3% or more of a 10-year probability for hip fracture, or a 10-year probability for other major osteoporotic fracture are 20% or more.

As there are currently no data of Thai population for FRAX measurement, the Thai Osteoporosis Foundation has initially studied and tested FRAX™ by referred data of Asian. Considering of osteoporosis epidemiology data for Thailand demonstrates that it is appropriate to use FRAX™ with Asian race including US-Asian and Japan. However it is suggested to use meeting point suggested by NOF — drug treatment can be used in patient with a 10-year probability for hip fracture of 3% or more or a 10-year probability for other major osteoporotic fractures of 20% or more.
II-3 Laboratory investigation and bone strength assessments

3.1 Laboratory investigation

Objective of laboratory investigation

1. To assure diagnosis of osteoporosis
2. To assess risk of osteoporosis
3. To determine causes of osteoporosis

Primary laboratory investigation

- Complete blood count (CBC)
- Serum calcium, phosphate, albumin and liver transaminases
- Serum alkaline phosphatase
- Renal function (blood urea nitrogen and creatinine)
- Plain x-rays suggested to check lateral thoraco-lumbar spine or antero-posterior hip in case of indicated or suspected of bone fracture

3.2 Bone strength assessment

Bone strength includes bone mass and bone quality which is not currently assessed accurately by any technologies for clinical uses, so bone density is mainly used for clinical assessment of bone strength.

1. Diagnosis using a plain x-ray is not enough sensitive to indicate decreasing of bone mass — to be visible on radiogram, bone mass must be decreased more than 30-40% of normal value.
2. Using semi-quantitative method to assess radiogram from a plain film x-ray, such as Singh’s index, cannot control assessment standard and because of highly intra-observer and inter-observer, it is not suggested to be used.
3. According to WHO standard, only dual-energy x-ray absorptiometry (DXA) can be used for bone mass measurements to diagnose osteoporosis
4. For diagnosis of osteoporosis, other technologies for bone mass measurements such as quantitative ultrasonography (QUS) or peripheral DXA (pDXA) cannot be used instead of DXA. However, these technologies are useful in screening people who have high risk of osteoporosis for further confirm diagnosing by DXA.
II-4 Diagnostic criteria for osteoporosis

4.1 Measurement of bone density

Bone mass density (BMD) can be measured by several following tools.

Dual Energy X-ray Absorptiometry

WHO diagnostic criteria\(^{(6,7)}\) representing in table 2.3 are used to diagnose osteoporosis in women by comparing measured BMD with maximum BMD in young women and considering lower value or one equal to 2.5 times of standard deviation for diagnosis of osteoporosis. Risk of bone fracture is increased 1.4-2.6 times for one time of decreasing of standard deviation.\(^{(8)}\) (Grade A, Level Ia)

Table 2.3 Diagnosis of osteoporosis using bone density measured by DXA

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Bone density is in normal level — one time minus of standard deviation or more comparing with maximum mean of bone mass in young women (T-score $\geq$ -1)</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Bone density is lower than one time minus and higher than two and a half times minus of standard deviation comparing with maximum mean of bone mass in young women (-2.5 &lt; T-score &lt; -1)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Bone density is lower than two and a half times minus of standard deviation comparing with maximum mean of bone mass in young women (T-score &lt; -2.5)</td>
</tr>
<tr>
<td>Severe/established osteoporosis</td>
<td>Bone density is lower than two and a half times minus of standard deviation comparing with maximum mean of bone mass in young women (T-score &lt; -2.5) including fragility fracture</td>
</tr>
</tbody>
</table>

Axial DXA, Lumbar spine or L-spine and hip are measured of BMD for diagnosis of osteoporosis. Peripheral DXA is important only for overweight patients or ones whom axial DXA is not available.

Standard value using in comparison must be maximum mean of bone mass in young women in the same race (female reference). For example, using Thai female reference for Thai women, however, using Asian, Japanese or Chinese female reference is also permit (Caucasian female reference is not be used).

The same standard is used in men (table 2.3) but in reference young adult mean — using male reference in the same race or neighboring instead of female reference.
**Indicator for BMD measurement by DXA**

1. Female age 65 and older and male age 70 and older
2. Female age under 65 and male age under 70 having at least 1 of following risk factors
   - Early menopause and those whose ovaries were removed before menopause
   - Keeping on estrogen deficiency more than a year before menopause except women with pregnancy and breast-feeding
   - Long term glucocorticoid intake (Prednisolone 7.5 mg/day or equal for above 3 months)
   - Parent history in hip fracture
   - Menopausal women with less body mass index than 19 kg/m²
3. Radiographic osteopenia and/or vertebral deformity by x-ray
4. History of bone fracture without severe accident
5. Decreasing in height
6. Vulnerable group by OSTA score\textsuperscript{10}, KKOS score\textsuperscript{11} or nomogram above 0.3 for menopausal women (see appendix 2.2)

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

**Quantitative Ultrasound (QUS)**

QUS role for both diagnosis and monitoring treatment are not clear. Diagnosis with only QUS has low sensitivity but high specificity. However, diagnosis with combination of QUS, OSTA\textsuperscript{10} and KKOS\textsuperscript{11} increases sensitivity and specificity. In addition, using combination of QUS, age and weight in nomogram, results in better prediction of osteoporosis. However, this method cannot be used as osteoporosis diagnosis.

**4.2 Biochemical markers of bone turnover**

As biochemical index of bone formation and resorption is changed by several factors, it is not suggested to use for diagnosis of osteoporosis. In addition, it may be unusual in several diseases, but it can be used combined with BMD to assess risk of bone fracture.\textsuperscript{14-16} However, the index is useful for treatment monitoring\textsuperscript{17} and treatment is suggested to be assessed after 3 months and a year. It can be used to assess response to treatment with rapid detection.

Biochemical index of bone resorption includes urinary deoxypyridinoline (DPD), urinary N-telopeptide (NTx) and serum C-telopeptide (CTx) while biochemical index of bone formation include bone specific alkaline phosphatase (BSAP), osteocalcin and N-terminal propeptide of type I procollagen (PINP)\textsuperscript{18}
4.3 Screening

Screening of osteoporosis with DXA in general population is not suggested because it is not reasonable in economic health, but screening with OSTA\(^{(10)}\) or KKOS\(^{(11)}\) is suggested because it is costless and can screen people who are in vulnerable group of osteoporosis for further examination of BMD (see appendix 2.1)

**Appendix 2.1**

OSTA (Osteoporosis Self-Assessment Tool for Asians)

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Weight (kg)</th>
<th>OSTA Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-44</td>
<td>40-44</td>
<td>Low Risk</td>
</tr>
<tr>
<td>45-49</td>
<td>45-49</td>
<td>Low Risk</td>
</tr>
<tr>
<td>50-54</td>
<td>50-54</td>
<td>Low Risk</td>
</tr>
<tr>
<td>55-59</td>
<td>55-59</td>
<td>Medium Risk</td>
</tr>
<tr>
<td>60-64</td>
<td>60-64</td>
<td>Medium Risk</td>
</tr>
<tr>
<td>65-69</td>
<td>65-69</td>
<td>High Risk</td>
</tr>
<tr>
<td>70-74</td>
<td>70-74</td>
<td>High Risk</td>
</tr>
<tr>
<td>75-79</td>
<td>75-79</td>
<td>High Risk</td>
</tr>
<tr>
<td>80-84</td>
<td>80-84</td>
<td>High Risk</td>
</tr>
<tr>
<td>85-89</td>
<td>85-89</td>
<td>High Risk</td>
</tr>
<tr>
<td>90-94</td>
<td>90-94</td>
<td>High Risk</td>
</tr>
<tr>
<td>95-99</td>
<td>95-99</td>
<td>High Risk</td>
</tr>
</tbody>
</table>

OSTA risk can be calculated by the formula of 0.2X (weight in kilograms - age in years) and the decimal is cut off.
**Result Evaluation**

OSTA index
- less than -4: Highly risk
- Between -4 to -1: Average risk
- Above -1: Low risk

Khon Kaen Osteoporosis study score (KKOS)\(^{(13)}\)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Score</th>
<th>Weight (kg)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 45</td>
<td>+ 7.5</td>
<td>&lt; 30</td>
<td>- 14</td>
</tr>
<tr>
<td>45 - 49</td>
<td>+ 6.0</td>
<td>30 - 34</td>
<td>- 12</td>
</tr>
<tr>
<td>50 - 54</td>
<td>+ 4.5</td>
<td>35 - 39</td>
<td>- 10</td>
</tr>
<tr>
<td>55 - 59</td>
<td>+ 3.0</td>
<td>40 - 44</td>
<td>- 8</td>
</tr>
<tr>
<td>60 - 64</td>
<td>+ 1.5</td>
<td>45 - 49</td>
<td>- 6</td>
</tr>
<tr>
<td>65 - 69</td>
<td>0</td>
<td>50 - 54</td>
<td>- 4</td>
</tr>
<tr>
<td>70 - 74</td>
<td>- 1.5</td>
<td>55 - 59</td>
<td>- 2</td>
</tr>
<tr>
<td>75 - 79</td>
<td>- 3.0</td>
<td>60 - 64</td>
<td>0</td>
</tr>
<tr>
<td>80 - 84</td>
<td>- 4.5</td>
<td>65 - 69</td>
<td>+ 2</td>
</tr>
<tr>
<td>85 – 89</td>
<td>- 6.0</td>
<td>70 - 74</td>
<td>+ 4</td>
</tr>
<tr>
<td>&gt; 90</td>
<td>- 7.5</td>
<td>75 - 79</td>
<td>+ 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80 - 84</td>
<td>+ 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>85 - 89</td>
<td>+ 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 90</td>
<td>+ 12</td>
</tr>
</tbody>
</table>

Calculation of KKOS: plus score of age (years) with score of weight (kilograms)

- **KKOS ≤ -1**: High risk of osteoporosis
- **KKOS > -1**: Low risk of osteoporosis

**Example:**

A Woman age 52, weight 48 kilograms

KKOS = (+ 4.5) + (-6) = - 1.5 ..=.. High risk

In addition, KKOS also estimates probability of osteoporosis as in the table — above 80% is defined as high risk, 21-79 is defined as average risk and 20% is defined as low risk.
Probability of osteoporosis using KKOS score

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>&lt; 45</th>
<th>45-49</th>
<th>50-54</th>
<th>55-59</th>
<th>60-64</th>
<th>65-69</th>
<th>70-74</th>
<th>75-79</th>
<th>80-84</th>
<th>85-89</th>
<th>&gt; 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>58.7</td>
<td>67.4</td>
<td>75.0</td>
<td>81.3</td>
<td>86.3</td>
<td>90.2</td>
<td>93.0</td>
<td>95.1</td>
<td>96.6</td>
<td>97.6</td>
<td>98.3</td>
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<tr>
<td>30-34</td>
<td>47.5</td>
<td>56.8</td>
<td>65.8</td>
<td>73.5</td>
<td>80.1</td>
<td>85.4</td>
<td>89.5</td>
<td>92.5</td>
<td>94.7</td>
<td>96.3</td>
<td>97.4</td>
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<td>36.6</td>
<td>45.6</td>
<td>54.9</td>
<td>63.8</td>
<td>71.9</td>
<td>78.8</td>
<td>84.4</td>
<td>88.7</td>
<td>91.9</td>
<td>94.3</td>
<td>96.0</td>
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<td>26.9</td>
<td>34.8</td>
<td>43.6</td>
<td>52.9</td>
<td>62.0</td>
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<td>77.5</td>
<td>83.3</td>
<td>87.9</td>
<td>91.3</td>
<td>93.9</td>
</tr>
<tr>
<td>45-49</td>
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<td>33.0</td>
<td>41.7</td>
<td>51.0</td>
<td>60.2</td>
<td>68.7</td>
<td>76.1</td>
<td>82.2</td>
<td>87.0</td>
<td>90.7</td>
</tr>
<tr>
<td>50-54</td>
<td>13.0</td>
<td>17.8</td>
<td>23.9</td>
<td>31.3</td>
<td>39.8</td>
<td>49.0</td>
<td>58.3</td>
<td>67.0</td>
<td>74.6</td>
<td>81.0</td>
<td>86.1</td>
</tr>
<tr>
<td>55-59</td>
<td>8.7</td>
<td>12.1</td>
<td>16.7</td>
<td>22.5</td>
<td>29.7</td>
<td>38.0</td>
<td>47.1</td>
<td>56.4</td>
<td>65.2</td>
<td>73.1</td>
<td>80.0</td>
</tr>
<tr>
<td>60-64</td>
<td>5.7</td>
<td>8.1</td>
<td>11.3</td>
<td>15.6</td>
<td>21.2</td>
<td>28.1</td>
<td>36.2</td>
<td>45.1</td>
<td>54.4</td>
<td>63.4</td>
<td>71.6</td>
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<td>5.3</td>
<td>7.5</td>
<td>10.5</td>
<td>14.6</td>
<td>19.9</td>
<td>25.5</td>
<td>34.4</td>
<td>43.2</td>
<td>52.5</td>
<td>61.6</td>
</tr>
<tr>
<td>70-74</td>
<td>2.4</td>
<td>3.4</td>
<td>4.9</td>
<td>7.0</td>
<td>9.8</td>
<td>13.7</td>
<td>18.7</td>
<td>25.0</td>
<td>32.6</td>
<td>41.3</td>
<td>50.5</td>
</tr>
<tr>
<td>75-79</td>
<td>1.5</td>
<td>2.2</td>
<td>3.2</td>
<td>4.6</td>
<td>6.5</td>
<td>9.2</td>
<td>12.8</td>
<td>17.5</td>
<td>23.6</td>
<td>30.9</td>
<td>39.4</td>
</tr>
<tr>
<td>80-84</td>
<td>1.0</td>
<td>1.4</td>
<td>2.1</td>
<td>3.0</td>
<td>4.2</td>
<td>6.0</td>
<td>8.5</td>
<td>11.9</td>
<td>16.4</td>
<td>22.2</td>
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<tr>
<td>85-89</td>
<td>0.6</td>
<td>0.9</td>
<td>1.3</td>
<td>1.9</td>
<td>2.7</td>
<td>3.9</td>
<td>5.6</td>
<td>7.9</td>
<td>11.1</td>
<td>15.4</td>
<td>20.9</td>
</tr>
<tr>
<td>&gt; 90</td>
<td>0.4</td>
<td>0.6</td>
<td>0.8</td>
<td>1.2</td>
<td>1.8</td>
<td>2.5</td>
<td>3.6</td>
<td>5.2</td>
<td>7.4</td>
<td>10.4</td>
<td>14.4</td>
</tr>
</tbody>
</table>

>80 High risk  21-79 Intermediate risk  <20 Low risk
Appendix 2.2

Nomogram for diagnosing osteoporosis in menopausal women using age, weight and QUS\textsuperscript{(15)}

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35</td>
<td>45</td>
<td>55</td>
<td>65</td>
<td>75</td>
<td>85</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>95</td>
<td>90</td>
<td>85</td>
<td>80</td>
<td>75</td>
<td>70</td>
<td>65</td>
<td>60</td>
<td>55</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>QUS</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>-1</td>
<td>-2</td>
<td>-3</td>
<td>-4</td>
<td>-5</td>
<td></td>
</tr>
<tr>
<td>Total Points</td>
<td>0</td>
<td>40</td>
<td>80</td>
<td>120</td>
<td>160</td>
<td>200</td>
<td>240</td>
<td>280</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear Predictor</td>
<td>-8</td>
<td>-6</td>
<td>-4</td>
<td>-2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Risk of Osteoporosis</td>
<td>0.01</td>
<td>0.1</td>
<td>0.3</td>
<td>0.6</td>
<td>0.8</td>
<td>0.95</td>
<td>0.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Calculation**

1. Draw a line of age up to a line of points
2. Draw a line of weight up to a line of points
3. Draw a line of QUS up to a line of points
4. Count all points (total points)
5. Draw a line of total points down to a line of risk of osteoporosis
6. In case that risk score of osteoporosis is above 0.3, it is defined as high risk and should be further estimated by BMD

**Example:**

A woman age 70, weight 50 kilograms and QUS T-scored -3 SD

The lines were drawn as in steps 1-3 resulting in 48, 67 and 78 points respectively. Total point was 193 (step 4) and a line of 193 total points was drawn down to a line of risk at score 0.5 (step 5)

Result evaluation: 50 of 100 women age 70, weight 50 kilograms and QUS T-scored -3 SD are likely to have osteoporosis.
Reference


17 Riggs B, Melton U, 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;18:197S-201S.
III Prevention of osteoporosis and falls

Prevention of osteoporosis defines as protecting bone mass from losing its density in osteoporosis-free person. Currently, preventive strategies for osteoporosis focus on non-pharmacological approaches because of the economical cost-effectiveness. Prevention of osteoporosis can be classified into two categories by age; one is the prevention in young population which focuses on reinforcement of bone mass density, another is the prevention in postmenopausal population, defined as men and women of the age 50 or more, which focuses on protection of bone mass from deterioration.

III-1 Strategies to maximize peak bone mass

Reinforcement of peak bone mass since childhood is the key to healthy and quality bone which can be achieved by;
1. Weight bearing exercise and resistive exercise
2. Sufficient calcium intake from food
3. Adequate sunlight exposure for vitamin D synthesis
4. Avoid some behaviors at risk of osteoporosis such as;
   4.1 smoking
   4.2 coffee and other caffeinated-drink consumption
   4.3 salty food and high-protein food
   4.4 alcohol consumption
5. Include more physical activities in the daily life
6. Good control of some chronic disease that affect the risk for osteoporosis
7. Avoid usage of some drugs that can increase the risk for osteoporosis
8. Keep the body mass index (BMI) between 20-23 kg/sq.m.

III-2 Strategies to prevent bone loss

After bone mass reaches the highest peak, the rate of bone formation will be slower than the rate of bone resorption. In postmenopausal women, the rate of bone resorption will be very rapid but the following strategies could help slower it down.
1. Non-pharmacological management which is all that described in III-1
2. Pharmacological management which will be implemented in the group with high risk of osteoporosis. Drugs and supplements to be prescribed are;
   2.1 Hormone replacements
   2.2 Calcium and Vitamin D
Hormone replacement therapy

1. Estrogen Therapy (ET) or Hormone [Replacement] Therapy (H[R]T). In postmenopausal women, these types of therapy are approved only for treatment of postmenopausal symptoms such as hot flashes, vaginal dryness in combination with prevention of osteoporosis (1-6). Prescribing estrogen replacement to women who have not gone hysterectomy must only be in combination with progestin to prevent uterine hyperplasia.

2. A Women Health Initiative (WHI) study (7) showed that co-treatment of conjugated equine estrogen (CEE) and mederoxy progesterone acetate (MPA) for at least 5 years can help reduce the incidence of vertebral and hip fractures with clinical symptoms for 34 % and 23% for other fractures.

3. WHI study also reported the side effects of estrogen therapy are increasing risks of breast cancer, deep vein thrombosis and cardiovascular diseases. However, when data from WHI study was re-evaluating, it turned out that co-treatment of CEE and MPA in women who undergone postmenopausal for less than ten years are beneficial for prevention of cardiovascular diseases. Moreover, a continuous treatment of estrogen therapy alone for 7.1 years decreases the risk of breast cancer as compared to women without hormone treatment. Nevertheless, there is no study regarding the risks and benefits of using other types of estrogen or progestin as compared to CEE and MPA, only an assumption is made that they should have the same risks and benefits as CEE and MPA. Therefore, it is recommended to use the lowest regimen for single or combined estrogen/progestin therapy with the possible shortest course of treatment that is effective (8, 9).

4. Usage of low dosage hormone therapy for a longer course of treatment in women who have hormone deficiency and at risk of osteoporosis can be done if the patient has been carefully informed with the risks and benefits of the treatment (9).

5. Termination of hormone therapy leads to 3-6% loss of bone mass per year. There are also data supports that after hormone therapy is terminated, the benefits of reduction for bone fractures incidence will be lost (catch-up phenomenon) and the incidence rate of bone fractures will increase to the level similar to people without hormone therapy in one-year after termination (10) so, this must be carefully considered before starting hormone therapy.

III-3 Nutritional aspects in osteoporosis

The important nutrients for the process of bone reinforcement are proteins, vitamin C, vitamin D, vitamin K and variety of minerals such as calcium, magnesium, copper, zinc, manganese and phosphorus.
**Calcium**

The recommended daily value of calcium intake according to U.S. NIH is shown in Table 3.1 (11).

**Table 3.1** Optimal calcium intake recommended for each age group by National Institutes of Health Consensus Panel

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Optimal Calcium Intake (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td></td>
</tr>
<tr>
<td>Birth – 6 months</td>
<td>400</td>
</tr>
<tr>
<td>6 months – 1 year</td>
<td>600</td>
</tr>
<tr>
<td>Children</td>
<td></td>
</tr>
<tr>
<td>1 – 5 years</td>
<td>800</td>
</tr>
<tr>
<td>6 – 10 years</td>
<td>800-1200</td>
</tr>
<tr>
<td>Adolescents/young adults</td>
<td></td>
</tr>
<tr>
<td>11 – 24 years</td>
<td>1200-1500</td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>25 – 50 years</td>
<td>1000</td>
</tr>
<tr>
<td>Over 65 years</td>
<td>1500</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>25 - 50 years</td>
<td>1000</td>
</tr>
<tr>
<td>Over 50 years (postmenopausal)</td>
<td></td>
</tr>
<tr>
<td>- On estrogen</td>
<td>1000</td>
</tr>
<tr>
<td>- Not on estrogen</td>
<td>1500</td>
</tr>
<tr>
<td>Over 65 years</td>
<td>1500</td>
</tr>
<tr>
<td>Pregnant and nursing</td>
<td>1200-1500</td>
</tr>
</tbody>
</table>


For the Ministry of Public Health of Thailand, in 2002, the daily optimal calcium intake for each age group is shown in Table 3.2.
Table 3.2 Optimal calcium intake recommended for each age group by Thailand Ministry of Public Health, 2002.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>Recommended Daily Optimal Calcium Intake (milligram)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>0-5 months</td>
<td>210</td>
</tr>
<tr>
<td></td>
<td>6-11 months</td>
<td>270</td>
</tr>
<tr>
<td>Child</td>
<td>1-3 years</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>4-8 years</td>
<td>800</td>
</tr>
<tr>
<td>Adolescent</td>
<td>9-18 years</td>
<td>1,000</td>
</tr>
<tr>
<td>Adult</td>
<td>19-50 years</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>Over 50 years</td>
<td>1,000</td>
</tr>
<tr>
<td>Pregnant woman*</td>
<td></td>
<td>800</td>
</tr>
<tr>
<td>Breast-feeding mother**</td>
<td></td>
<td>800</td>
</tr>
</tbody>
</table>

* Pregnant and breast-feeding adolescent should take calcium according to the recommendation for adolescent.
** In case of inability for breast-feeding, Infant Formula milk or Follow-up formula milk should be given.
*** one cup of milk or 1 pack of milk (200 milliliter) has 230 milligram of calcium.

A study in Japanese male and female elders by balance study (12) showed that in daily consumption of 702 mg in elderly males and 788 mg in elderly females is adequate. However, supplementation of another 20% of those will be good for body reinforcement therefore, in elderly male, a recommended daily value for calcium intake is 842 mg and for female elders is 946 mg.

The recommended calcium value should be consumed firstly from food and then supplemented by calcium tablets. Low calcium intake leads to resorption of calcium from bone and teeth and collectively increases the risks for osteoporosis or oral cavities.

High-calcium containing foods are ubiquitous especially in local foods as shown in Table 3.3.
Table 3.3 Calcium amount in daily meal of Thais

<table>
<thead>
<tr>
<th>Types of food</th>
<th>Amount consumed</th>
<th>Calcium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh milk, UHT milk, Pasteurized</td>
<td>200 CC (1 pack)</td>
<td>240</td>
</tr>
<tr>
<td>milk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yogurt milk</td>
<td>150 CC (1 cup)</td>
<td>150</td>
</tr>
<tr>
<td>Dried small prawn</td>
<td>1 tablespoon (tbsp)</td>
<td>145</td>
</tr>
<tr>
<td>Dried small shrimp</td>
<td>1 tbsp</td>
<td>167</td>
</tr>
<tr>
<td>Shrimp paste</td>
<td>2 teaspoon (tsp)</td>
<td>156</td>
</tr>
<tr>
<td>Dried anchovy</td>
<td>½ cup</td>
<td>76</td>
</tr>
<tr>
<td>Fish ball</td>
<td>10 balls</td>
<td>52</td>
</tr>
<tr>
<td>Dried fish</td>
<td>1 fish</td>
<td>106</td>
</tr>
<tr>
<td>Duck egg</td>
<td>1 egg</td>
<td>78</td>
</tr>
<tr>
<td>Chicken egg</td>
<td>1 egg</td>
<td>63</td>
</tr>
<tr>
<td>Quail egg</td>
<td>1 egg</td>
<td>30</td>
</tr>
<tr>
<td>Sesame</td>
<td>1 tsp</td>
<td>116</td>
</tr>
<tr>
<td>Red bean (raw)</td>
<td>1 tsp</td>
<td>97</td>
</tr>
<tr>
<td>Tofu</td>
<td>1 piece</td>
<td>240</td>
</tr>
<tr>
<td>Soy bean (cooked)</td>
<td>10 tbsp</td>
<td>245</td>
</tr>
<tr>
<td>Mung bean (cooked)</td>
<td>10 tbsp</td>
<td>125</td>
</tr>
<tr>
<td>Noni leaves</td>
<td>1 cup</td>
<td>469</td>
</tr>
<tr>
<td>Tamarind pod (fresh)</td>
<td>10 pods</td>
<td>429</td>
</tr>
<tr>
<td>Kale</td>
<td>1 cup</td>
<td>230</td>
</tr>
<tr>
<td>Green peas</td>
<td>1 cup</td>
<td>49</td>
</tr>
<tr>
<td>Turkey berry</td>
<td>1 cup</td>
<td>299</td>
</tr>
<tr>
<td>Parkia</td>
<td>1 cup</td>
<td>76</td>
</tr>
<tr>
<td>Types of food</td>
<td>Amount consumed</td>
<td>Calcium (mg)</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Taro</td>
<td>4 tbsp</td>
<td>17</td>
</tr>
</tbody>
</table>

**From:** Dr. Surat Komindara, department of internal medicine, faculty of medicine, Ramathibodhi hospital.

**Vitamin D**

1. Vitamin D is an important hormone that acts in concert with other hormones to maintain balanced levels of calcium and phosphorus in body. Vitamin D induces the absorbance of calcium and phosphorus in the intestine and also works with parathyroid hormone to control the level of calcium and phosphorus in blood. Vitamin D can also enhance the process of calcium resorption from bone to blood circulation. In addition, vitamin D is a key player in bone formation and mineralization.

2. There are 2 sources of vitamin D, one is from the foods such as milk and fish oil, another source is from the vitamin D synthesis at the skin by ultraviolet B (UVB) exposure from sunlight.

3. Natural vitamin D are ergocalciferol found in plants and cholecalciferol from animals however these two types of vitamin D is not in their active form and needed to be activated by addition of OH group at 2 positions, first at position 25 to become 25-hydroxyvitamin D (25(OH)D or calcidiol. Then calcidiol undergoes second addition of OH group take place in kidney, at position 1 of the molecule and become 1,25-dihydroxyvitamin D (1,25(OH)2D or calcitriol or vitamin D3 which is the active form of vitamin D.

4. In elderly people, vitamin D and calcium metabolism undergo variety changes such as:
   - Synthesis of 7-dehydrocholesterol, precursor of vitamin D3 at the skin of elderly people decreases therefore the total vitamin D3 reduces.
   - Reduced intake of vitamin D from food and decreased sunlight exposure since elderly people usually stay in house.
   - Reduced renal functions that leads to less 1, 25(OH)2D synthesis.
   - Reduced rate of calcium absorpti on in the intestine and decreased adaptability of the intestine to low calcium level.
   Because of these factors, elderly people are at risk of vitamin D deficiency that leads to secondary hyperparathyroidism, increase bone resorption and finally osteoporosis.

5. A study in Northeastern Thais (13, 14) found that most of them are having vitamin D deficiency however, recommendations from various institutes suggests that a supplement of vitamin D for 400-800 IU daily is adequate for protection of vitamin D deficiency.
Table 3.4 Vitamin D level in Foods

<table>
<thead>
<tr>
<th>Food</th>
<th>International Units (IU) per serving</th>
<th>Percent DV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod liver oil, 1 Tablespoon</td>
<td>1,360</td>
<td>340</td>
</tr>
<tr>
<td>Salmon, cooked, 3 ounces</td>
<td>360</td>
<td>90</td>
</tr>
<tr>
<td>Mackerel, cooked, 3 ounces</td>
<td>345</td>
<td>90</td>
</tr>
<tr>
<td>Tuna fish, canned in oil, 3 ounces</td>
<td>200</td>
<td>50</td>
</tr>
<tr>
<td>Sardines, canned in oil, drained, 1 ounces</td>
<td>250</td>
<td>70</td>
</tr>
<tr>
<td>Milk, nonfat, reduced fat, and whole, vitamin D fortified, 1 cup</td>
<td>98</td>
<td>25</td>
</tr>
<tr>
<td>Margarine, fortified, 1 Tablespoon</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>Pudding, prepared from mix and made with vitamin D fortified milk, cup</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>Ready-to-eat cereals fortified with 10% of the DV for vitamin D, 1 cup servings (servings vary according to the brand)</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Egg, 1 whole (vitamin D is found in egg yolk)</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Liver, beef, cooked, 3 ounces</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Cheese, Swiss, 1 ounce</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: * DV = daily value. DVs are reference numbers developed by the Food and Drug Administration (FDA) to help consumers determine if a food contains a lot or a little of a specific nutrient. The DV for vitamin D is 400 IU (10 μg) for adults. Most food labels do not list vitamin D content unless a food has been fortified with this nutrient.


Vitamin K

1. Natural vitamin K exists in two types which are Vitamin K-1 or phylloquinone from plants and Vitamin K-2 or menaquinone which is synthesized in the large intestine of animals.
2. All green vegetables synthesizes phylloquinone. Phylloquinone is a composite of chloroplasts while the normal flora in animal intestine and some spore-forming Actinomycetes spp. can synthesize menaquinones.
3. There is high concentration of vitamin K found in green vegetables while low level of vitamin K is found in fruits and grains. In meat and milk, vitamin K is found in medium level.
4. Normal flora in human intestine can synthesize menaquinone but the uptake of vitamin K is by passive diffusion therefore the gaining of vitamin K via this mechanism are not enough.

5. Osteoblast releases collagen matrix and a non-collagen matrix called osteocalcin. Newly released osteocalcin is undercarboxylated and not in its active form. Undercarboxylated osteocalcin (ucOC) is then carboxylated to be mature osteocalcin or carboxylated osteocalcin (Gla protein) which can happen only with vitamin K presence. New active osteocalcin is the key molecule that binds to and brings calcium into bones resulting in mineralization. Hence, increased ucOC level reflects low of deficiency of vitamin K and leads to abnormal bone formation, low bone mass density and increase bone fragility. The level of ucOC can be used to predict the risk for hip fractures in elderly women.

6. In Thai, there is a study of ucOC in which the level of ucOC of 2.314 ng/ml indicates the vitamin K deficiency (15). Also this study found that 39.1% of participating elderly women have ucOC level more than 2.314 ng/ml or having vitamin K deficiency. Moreover, in elders who have ucOC level over 2.314 ng/ml tend to have bone mass density at ultradistal radius and distal 1/3 of radius and 25(OH)D level significantly lower than elders that have normal ucOC level (p<0.05).

7. According to Thai Recommended Daily Intakes (RDI) for people with the age over 6 years made by the Advisory Board for Nutritional Facts Display 1996, it suggests daily vitamin K intake of 80μg which are less than what is recommended in U.S. which are 3μg per kilogram body weight or approximately 70-140μg for adults.

8. Deficiency for other minerals such as magnesium, copper, zinc, manganese and phosphorus is rarely found in normal population except in patients with gastrointestinal tract disease such as alcoholism and intestinal abnormalities.
Table 3.5 Vitamin K level in Foods

<table>
<thead>
<tr>
<th>Types of Food</th>
<th>Vitamin K level (µg/100g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kale</td>
<td>817</td>
</tr>
<tr>
<td>Spinach</td>
<td>400</td>
</tr>
<tr>
<td>Endive</td>
<td>231</td>
</tr>
<tr>
<td>Broccoli</td>
<td>205</td>
</tr>
<tr>
<td>Cabbage</td>
<td>147</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>193</td>
</tr>
<tr>
<td>Rapeseed oil</td>
<td>141</td>
</tr>
<tr>
<td>Regular natto</td>
<td>775</td>
</tr>
</tbody>
</table>

III-4 Life style modification and prevention of falls

4.1 Modification of risk behaviors for osteoporosis

The following behaviors/foods should be adopted to reduce the risks for osteoporosis.
- Avoid smoking behavior
- Avoid consummation of coffee and caffeinated drinks
- Avoid consummation of salty and high-protein foods
- Avoid over consumption of alcohol beverages
- Have more physical activities
- Control of chronic symptoms at risks of osteoporosis
- Be careful on using drugs that increase the risks of osteoporosis

4.2 Prevention of falls in patients with osteoporosis

Patients with osteoporosis are the population at risks of having bone fractures because of reduced bone mass density and changes in bone tissues however, bone fracture are normally the results of falls which the incidence increased as aging. Annually, one third of people with age over 65 and half of people of the age over 80 have fallen at least once (16). Moreover, elders admitted in hospital have three times more incident rate than elders who live somewhere else. Also, elders with history of fall tend to have 2-3 times more
likely to fall again. Strikingly, almost 40% of elders have fallen more than 1 time a year (17). From these data, it is obvious that falls is one of the major problems in elderly people. In addition, fall is the major reason for hospital admission of elderly people, the incidence of fall as a cause of hospital admission is five times more than the other causes. Consequently, if elderly patients have hip fractures from falls, it is likely that they will have to be in a hospital longer that results in higher cost of hospital admission and treatment. As an impact to longer hospital admission and disability from hip fractures, other inconvenient issues physically, mentally, economically and to quality of life may have followed. Half of the elderly patients that have been admitted to hospital because of hip fractures can never be discharged and be able to help themselves to daily rituals anymore (18). Also, this may result as early death. Therefore, it is vital to prevent fall in osteoporotic elders.

**Risk factors for fall**

There are number of studies regarding the risk factors of fall such as weaken thigh muscles, adhesive joints especially leg joints, walking abnormalities, loss of body balance, poor visualization, psychotropic or sedative treatment, low blood pressure, scare to fall and unsafe environment.

1. It is widely accepted that fall is the results from multiple factor rather than single factor. In patients with multi-factor for fall, they will have more risks than of people without any fall factor, from 8-10% to 69-78% in people with four or more risks (19, 20). Apart from that, there is a multivariate analysis of fall risk factors found that only three risk factors lead to fall (21) which are weaken hip muscles, loss of body balance and taking of 4 or more drugs altogether. In people with none of these 3 factors, only 12% may fall while in people with these 3 factors will probably fall 100%.

2. In summary, the risk factors for fall are very crucial and must be carefully explored to maximize the preventive scheme for fall. All factors from inside the patient and outside should be concerned such as;

**Intrinsic factors**

- History of fall (22,23)
- Malnutrition (24)
- Cognitive impairment (25)
- Impaired visual (26)
- Imbalance walking behavior (27)
- Combined drug usages (25)
- Other complications (27) such as diabetes mellitus, paralysis from strokes, foot problem, low blood pressure.
- Weaken muscles or impaired body balance (28)

- Fear from fall (18)
Extrinsic factors
- Environmental factors (29) such as electrical wire on floor, inadequate light, slippery floor, un leveled floor or in bathroom without hand rail.
- Types of clothes and shoes
- Inappropriate usage of walking devices

Prevention of fall

Prevention guidelines may be different between one for healthy elders and one for frail elders. However, below guidelines should be followed.

1. Searching for the group of people at risks for fall to raise awareness from caretaker of these people by first, using the falls risk assessment tools (31) which can separate the people at risk into 3 levels, high risk, medium risk, and low risk according to the score (see appendix 3.1). The score of 0-10 will be in low risks group, 11-20 scores is medium risks group and 21-33 scores is high risks group. The recommended period for assessment is when the person is admitted to the hospital or having a fall or at least every 3 months.

2. Additionally, the ability to keep body balanced should also be tested. For this aspect, the Berg balance scale (32), 180 degree turn (33) or functional reach (34) can be used for testing but some tests may not be appropriated for used in a clinic therefore a development of “timed up & go test (TUGT)” (35) is created. TUGT is a process that a patient has to stand up from sitting position and walk for a distance of 3 meters then turn back and walk back to sit at the same chair. The advantage of this test is that no special equipment is required and it is easy to be done in a clinic for elderly and the normal value should not exceed 10 seconds (36).

3. Reconsider the usage of multiple drugs at a time since there are reports for co-treatment of 3 or 4 drugs can increase risks for fall and can cause nine times more of impaired cognate (37). Even treatment of a single psychotropic drug such as sedatives, anti-depressants, sleeping pills or drugs that have dehydration as a side effect such as diuretics or laxatives. Also the usage of drugs in benzodiazepine group can also increase the fall incidences of 44% (39). Therefore, reconsideration of the drug regimen to the minimum requirement will be most beneficial to patients (40).

4. Since some of the most important risk factors for fall are weaken muscles and impaired body balance therefore exercise is a mean that has been proved to be beneficial in prevention of fall (41). Balance training, strengthening exercise and cardiovascular fitness training not only are advantageous for stronger muscles and better body balance but also induce bone formation which is very valuable for osteoporotic patients (40) (see appendix 3.2).

5. Correction of shoes and foot problems. The foot problem that usually observed with the problem of fall is foot ache, high-arched foot, warts or corns, slanted
toes, swelling foot, etc. Some problem may cause from uncomfor ted shoes. The recommended shoes are flats or have heels that its height is not higher than 2.5 cm. Good shoes should have firm heel counter and it is better to have a rubber support rather than leather support because it prevents slippery and is light-weighted. The front of shoes should be wide enough for all toes to sit in it comfortably. The length of foot and shoes when measured in standing position should have at least 1 cm space left. The frontal part should be soft and the shoes must be comfortable and well-fitted.

6. Environmental assessment. In many circumstances, fall may be happened because of environmental factors such as inadequate light, unlevel floor, slippery floor, untidy things on the floor, rugs and unfamiliar with furniture around the house or environmental changes. Fall accidents often take place in slippery bathroom therefore installation of a hand rail inside the bathroom should be considered.

7. Eye sight and visualization assessment. Elderly people commonly have eye problems such as cataract, diabetes eyes, glaucoma which will interfere the eye sight especially when combined with deterioration of central nervous system, will increase the fall incidence (44). Hence, osteoporotic patients should consult ophthalmologist.

8. Instructions for fall prevention should be given to both patients and caretakers. They should be informed of possible risks for fall and prohibitions from some daily activities. Patient should also be informed of how to change each position slowly and must be familiar with the living environment, regardless of whether the environment at home or at hospital. Patients should be informed such that they know how to primarily exam themselves if they fall before asking for help.
### Appendix 3.1 Fall Risk Assessment Tools

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days after hospital admission</td>
<td>First</td>
<td>The first seven days</td>
<td>8-14 days</td>
<td>Over 14 days</td>
</tr>
<tr>
<td>Age</td>
<td>0-19 years</td>
<td>20-59 years</td>
<td>60-70 years</td>
<td>Over 70 days</td>
</tr>
<tr>
<td>History of fall</td>
<td>None</td>
<td>One fall within 6 months</td>
<td>One fall within 3 months</td>
<td>One fall within last month</td>
</tr>
<tr>
<td>Body balance</td>
<td>Be able to stand and turn around with some help</td>
<td>Walk with walking assistance device or need help from 2 persons</td>
<td>Walk with walking assistance device or need help from one person</td>
<td>Walk without device or any help</td>
</tr>
<tr>
<td>Awareness</td>
<td>Aware of time, place and person</td>
<td>Aware of place and person</td>
<td>Aware of person</td>
<td>None, impaired decision ability</td>
</tr>
<tr>
<td>Physical conditions</td>
<td>Have enough food and drinks</td>
<td>No appetite, abnormal sleeping</td>
<td>Increasing abnormal sleeping</td>
<td>Malnutrition, weight-loss</td>
</tr>
<tr>
<td>Visualization</td>
<td>Normal</td>
<td>With lenses</td>
<td>Unclear visual, cataracts</td>
<td>Impaired visual up to blindness</td>
</tr>
<tr>
<td>Speech</td>
<td>Normal</td>
<td>Problems with speaking but good understanding</td>
<td>Impaired speaking or have trouble with communication</td>
<td>Seriously impaired communication</td>
</tr>
<tr>
<td>Drug usage</td>
<td>No affecting drug</td>
<td>Cardiovascular medicine such as β-blockers, diuretics, anti-hypertension</td>
<td>Psychotropic drugs such as sedatives, sleeping pills, psychoactive drugs</td>
<td>Both cardiovascular medicines and psychotropic drugs</td>
</tr>
<tr>
<td>Chronic symptoms</td>
<td>None</td>
<td>1 symptom</td>
<td>&gt;1 symptom</td>
<td>Multiple symptoms</td>
</tr>
<tr>
<td>Uncontrolled defecate</td>
<td>No problem</td>
<td>Frequent urination</td>
<td>Nocturnal urination or stress incontinence</td>
<td>Urge incontinence, indwelling catheterization</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------</td>
<td>--------------------</td>
<td>------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td><strong>0-10 = low risk, 11-20 = medium risk, 21-33 = high risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**From:** Fall prevention: Best Practice Guidelines, Quality improvement and Enhancement Program, version 3, 2003

**Appendix 3.2 Recommended exercises for prevention of osteoporosis**

Exercises that are beneficial for bone mass density and increasing bone mass that is popular are weight bearing exercises such as
- Walking
- Jogging
- Aerobic dance
- Dancing
- Tai-Chi or Chi-Gong

To also be benefit from aerobic exercise, the exercise length should be 20-30 minutes for 3-5 times a week.

There are other studies show that exercise with resistance in elders and osteoporotic patients helps maintain and reinforce bone density for 1-3% (45-49). However, the resistance exercise should be practiced for the following muscles;
- Rotator cuff
- Pectoralis major
- Biceps
- Triceps
- Wrist flexors and wrist extensors
- Hip extensors
- Hip flexors
- Quadriceps
- Hamstrings
- Back extensors
- Abdominal muscles

The methods of exercise can be weight-lifting, rubber-stretching or weight-lifting instrument for variety of muscles available in the gym.
Exercises for increase bone mass and reduction of bone resorption

Undoubtedly, exercises and sports help increase bone mass and bone strength in young people. Boys who exercise everyday for 40 minutes have 9% more bone density and 12% more bone strength than boys who never exercise. In girls who work out everyday have 7% more bone density and 9% more bone strength than girl who never work out.

Prevention of fall and reduced chance of bone fracture incidence

In every year, 30% of people over 65 years old fall. But people who exercise regularly, at least 2 hours a week have reduce incidence rate of fall. There is a study showed that women who sit at desk for more than 9 hours per day tend to have 50% chance of having hip fractures as compared to women who sit at desk for less than 6 hours. There is also a study of elderly people in China who practice Tai-Chi regularly for 6 months have 70% less chance for fall.

There is also another exercise called vibratory exercises which is currently an interesting subjects for study its benefits to osteoporosis but the results are not quite cleared and will need another 2-3 years to conclude.
Reference


10 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.


IV Treatment of osteoporosis

IV-1 Goal of osteoporosis treatment

1.1 Definitions of osteoporosis prevention and treatment

**Osteoporosis protection**

Osteoporosis prevention defined as prescription of drugs or any interventions to people who have not yet experienced osteoporosis (according to WHO guidelines for diagnosis of osteoporosis part II-4) and have never suffered from osteoporotic fracture. The objective of osteoporosis prevention is to protect the person from or delay the onset of having osteoporosis.

**Osteoporosis treatment**

Osteoporosis treatment defined as prescription of drugs or any interventions to person who have osteoporosis (according to WHO guidelines for diagnosis of osteoporosis part II-4) and/or have had osteoporotic fracture with the objective to prevent the person from having his/her first osteoporotic fracture and/or subsequent fractures.

In other words, treatment of osteoporosis is to prescribe drugs or any interventions to patients with osteoporosis to prevent them from osteoporotic bone fractures.

1.2 The objectives of osteoporosis treatment

The main goals for osteoporosis treatment are;
1. Reduce the risks for bone fractures, regardless of the positions where fractures occur.
2. Decrease or stop overly bone resorption and/or promote bone formation in order to strengthening the bone and prevent fracture.
3. Improve quality of life for osteoporosis patients by;
   a. reduce pain
   b. keep body movement to normal
   c. reduce need for help

However, the most important goal of osteoporosis treatment is to reduce the risk of osteoporotic fractures and the ultimate goal of all drugs and interventions for osteoporosis must be proved to possess anti-fracture efficacy.

1.3 Guidelines for treatment of osteoporosis by “case-finding” strategy provided by International Osteoporosis Foundation and National Osteoporosis Foundation.

The most popular guidelines for treatment of osteoporosis to date is called “case-finding” strategy developed by two international osteoporosis treatment agencies named;
1. **International Osteoporosis Foundation** suggests the usage of clinical risk factors (CRFs) (2) which is used by WHO to invent the tools for prediction of osteoporotic fractures within 10 years called “FRAX” (3) described in part II-2.

2. **National Osteoporosis Foundation** who, in 2008, modified the guidelines by implementation of FRAX tool to osteoporotic fracture risk assessment and treatment by medicine (4). If the probability for having osteoporotic hip fracture with in 10 years turns out to be 3% or more or 20% or more for other bone fractures, the treatment may be given except for the following two scenarios which the treatment by drug prescription can be given without FRAX pre-assessment which are;

   a. Men or women with the age over 50 years with either spine or hip fractures.
   b. Men or women with the age over 50 years who have bone mass density at vertebrae or hips of T-score equal or less than -2.5 measured by DXA machine.

1.4 Guidelines for treatment of osteoporosis by case-finding strategy provided by Thailand’s Osteoporosis Foundation.

**Primary indications**

For postmenopausal women and men aged over 50 years, the treatment for osteoporosis must be given if the following signs are observed.
1. Have spine or hip fracture caused by minor accident.
2. Have the lumbar spine bone mass density (BMD) or the femoral neck BMD or the total hip BMP of T-score equal or less than 2.5 measured by axial DXA machine.

**Secondary indications**

In case with no history of spine or hip fracture and the measurement of bone mass density by axial DXA with T-score between <-1.0 and >-2.5 at lumbar spine, femoral neck or total hip which indicate the state of thin bone concurrent with another indications from below, the treatment of drugs should be given.
1. Having at least one bone fractures in positions other than spine and hip caused by minor accident happened after 40 years of age such as wrist fracture, pelvic fracture, distal femur or proximal tibial fracture, proximal humeral fracture, ankle fracture, etc.
2. Receiving glucocorticoid drugs with the dosage similar to predisolone of 7.5 mg daily longer than 3 months.
3. Having the diseases that can cause secondary osteoporosis such as type-1 DM, thyrotoxicosis, rheumatoid arthritis, SNSA (seronegative spondyloarthropathy), etc.
4. Evaluated by FRAX™ of US-Asian or Japan without inclusion of BMD of “10 year probability of hip fracture” equal or less than 3% or of “10 year probability of other major osteoporotic fractures” of equal or less than 20%.
5. Have clinical risk factors (CRFs) of two or more of the followings;
   a. Women with the age of 65 years or more or men with the age of 70 years or more.
   b. Have body mass index of less than 19 kg/sq.mm.
   c. Have the family history (from mother or father) of osteoporotic fracture.
   d. Enters postmenopausal before 45 years of age.
   e. Have smoking habit.
   f. Have alcohol-consumption habit.

In case that measurement of bone mass density by axial DXA cannot be done, it is not recommended to initiate the treatment with only data from the following indications;
- CRFs alone
- BMD assessment (from other machines than axial DXA) alone

This is because the information is not sufficient to initiate the treatment and will cause subsequent problems due to unnecessary treatment (over treatment) and cost-ineffectiveness regarding health economy.

In case that measurement of bone mass density by axial DXA cannot be done because the patients live in the rural area where referral is not an option, it is recommended to treat osteoporosis by the following indications;
1. Having spine or hip fractures.
2. Women over 65 or men over 75 years of age having fractures at other positions caused by minor injury with the following indications;
   - Diagnosed by radiologist to have thin bone by X-ray.
   - Evaluated by FRAX™ of US-Asian or Japan without inclusion of BMD of “10 year probability of hip fracture” equal or less than 3% or of “10 year probability of other major osteoporotic fractures” of equal or less than 20%.

**IV-2 Pharmacological treatment of osteoporosis**

Before decision to use pharmacological treatment for osteoporosis is made, a doctor should consider the drug’s mechanism of actions, clinical trial data in human for anti-fracture efficacy, potential of adverse events and most important, the therapy must be carefully tailored for each patient since each individual may response to the same therapy differently.

The main goal for osteoporosis treatment is prevention of bone fracture thus the anti-fracture efficacy of the drug must always be considered.

The anti-fracture efficacy means that the evaluation in clinical trial phase-III clearly shows that the particular drug has relative risk reduction as compared to placebo. In case of drugs in bisphosphonates group, a bridging study between the same drugs but different dosages can also be considered. The bridging study is when the bisphosphonate
with different dosage has been proved for anti-fracture efficacy; the new dosage can be prescribed if it is shown to improve bone mass density of the patients to the same level.

2.1 Inhibitors of bone resorption

**Bisphosphonates**

1. Bisphosphonates is the group of drugs that can inhibit bone resorption with the highest strength in the market now. Bisphosphonates can be divided into 2 groups which are the group of simple bisphosphonates and the group of nitrogen-containing bisphosphonates (5).

2. It was found that nitrogen-containing bisphosphonates can inhibit osteoclastic bone resorption stronger than the other group. In Thailand, there are 8 regimens of bisphosphonate that are approved by Thai FDA which are Alendronate (10mg) and Risedronate (5mg) (daily), Alendronate Once Weekly (70mg) and Risedronate Once Weekly (35mg) (once a week) and Ibandronate Once Monthly (150mg) (every month). Other regimens are Alendronate plus (contains 70mg of Alendronate and 2800 i.u. of Cholecalciferol) once a week, Ibandronate injection (3mg, i.v. injection every 3 months) and Zoledronate injection (5mg, IV infusion once a year)

**Estrogen and/or Progestin**

1. Estrogen helps decrease the rate of bone resorption in postmenopausal women. Many studies have shown that treatment of estrogen can reduce the risks for spine, hips and other bones fractures of 30-40% (6, 7).

2. Recent findings showed that low level of estrogen treatment is beneficial for bones in most female population as compared to its efficacy, safety and cost-effectiveness hence estrogen may be prescribed to postmenopausal women with high risks of bone fracture. Also, there is no prohibition in using estrogen in younger than 55 years old and in women with premature menopause.

3. Treatment of estrogen in women over 60 years of age for the single purpose of bone fracture prevention must be carefully considered case by case. Prolonged treatment of estrogen in elderly women may increase the risks for cardiovascular diseases, stroke and invasive breast cancer (8).

4. Progestin may be used in combination with estrogen, especially in women who still have uterus to prevent endometriosis and endometrial cancer only.
Selective estrogen receptor modulators (SERMs)

1. SERMs are non-steroid substances that can bind to estrogen receptor. They act differently as either estrogen agonist or antagonist in different tissues. Raloxifene is the only SERM that is approved by Thai FDA to be used for osteoporosis in postmenopausal women.
2. A study found that treatment of raloxifene can prevent the loss of bone tissue in postmenopausal women and reduce the risks for spine fracture for 30-50% in women who have thin bone or osteoporosis with or without history of spine fracture. In addition, from this study, raloxifene treatment did not prevent other fractures.
3. Raloxifene has other benefits such as decrease risks for invasive breast cancer for 60% but has no effect on cardiovascular diseases and stroke\(^{(10, 11)}\).

Nasal spray calcitonin

1. Calcitonin is a hormone produced by C-cells of the thyroid gland. Calcitonin binds to calcitonin receptor of osteoclast and inhibits bone resorption.
2. A study compared between salmon calcitonin in the nasal spray format of 100, 200 and 400 IU daily and placebo found that salmon calcitonin of 200 IU daily, administered by nasal spray, can reduce the incidence of spine fracture for 36%. However, 100 IU and 400 IU of salmon calcitonin, administered by nasal spray have the same effect as placebo (response ration = 0.64). Also salmon calcitonin cannot prevent other non-vertebral fractures or hip fracture\(^{(12)}\).
3. Salmon calcitonin in both nasal spray and intramuscular injection can reduce pain caused by vertebral fracture with the same efficacy as NSAIDs\(^{(13)}\).

2.2 Stimulators of bone formation

Recombinant human parathyroid hormone 1-34 (Teriparatide, TPTD)

1. A prospective, randomized, double-blind, multinational, placebo-controlled in 1,637 postmenopausal women who already had spine fractures for assessment of TPTD efficacy in reduction of new bone fracture\(^{(14)}\) found that during the period of 3 years of study, treatment of 20 µg TPTD daily (n=541) can reduce the incidence of new bone fractures for 65% and 53% for non-vertebral fractures as compared to 40µg daily treatment of TPTD (n=552) or placebo (n=544).
2. The meta-analysis for an assessment of TPTD for pain-reducing effect in osteoporotic patients who already have bone fractures found that treatment of 20 and 40µg of TPTD reduced the number of patients who have severe and
normal back pain as compared to bone resorption inhibitors such as biphosphonates and hormone therapy \(^{(15)}\).

3. In a carcinogenicity study, 24 months treatment of TPTD in a dosage of 20 times more than human in 344 Fischer mice found that there was a dose-dependent increase of osteosarcoma \(^{(16)}\). However, there was no incidence of osteosarcoma found in human subject who had been treated for TPTD for the longest of 25 months \(^{(14)}\).

4. The recommended dose of TPTD is 20µg intradermal injection daily. The injection should take place at the same time of the day but is recommended for before sleeping time and should not be used for longer than 2 years.

Since TPTD is an expensive drug and has potential long-term side effects, prescription of this drug should be more strictly than other treatment for osteoporosis.

**Special indications for teriparatide for treatment of osteoporosis**

Teraparatide can be prescribed only in the case of severe osteoporosis and high risk of having new bone fractures and in patients with the age over 65 and must have one of the following indications.

1. BMD T-score by axial DXA of fracture-free lumbar spine or femoral or total hip of \(\leq -2.5\) SD and having osteoporotic spinal fracture at two or more vertebrae.
2. BMD T-score by axial DXA of fracture-free lumbar spine or femoral or total hip of \(\leq -2.5\) SD and having osteoporotic hip fracture.
3. BMD T-score by axial DXA of fracture-free lumbar spine or femoral or total hip of \(\leq -3.5\) SD with spinal fracture at one or more vertebra.
4. Have evidence of inadequate response for bisphosphonate treatment \(^{(17)}\) with both of the following indications.
   - Have new vertebral fracture of one or more position or worsen current spine fracture or having new hip fracture. However, the patient must have bisphosphonate treatment of longer than 2 years.
   - Lumbar spine BMD have decreased for \(\geq 3\%\) per year or decrease of total hip or femoral hip BMD of \(\geq 5\%\) per year by calculation from least significant change-LSC \(^{(17,18)}\) after the treatment of bisphosphonate for longer than 2 years.

In the fourth indication, the dosage of bisphosphonate treatment must be evaluated such that the patients are with good compliance and persistence.

Moreover, teriparatide must be always used with strict compliance with part IV-4.75.
2.3 Mixed action agents

**Vitamin D and Vitamin D analogue**

1. Vitamin D or vitamin D analogue can help reduce the incidence of bone fracture only when given with calcium. The dosage of vitamin D must not be less than 800 IU in combination with no less than 1,000mg of calcium (19).
2. Supplement of vitamin D or vitamin D analogue with calcium is slightly beneficial for reduction of hip or other non-vertebral fractures (< 20%) but is not beneficial for vertebral fracture (19).
3. However, the patients who receive treatments for osteoporosis should receive adequate amount of calcium and vitamin D.

**Menatetrenone**

1. There are evidences showing that patients with high vitamin K intake have less incidence of hip fracture than patients with lower vitamin K intake (20, 21). Also, persons who have low vitamin K intake usually have lower BMD (22).
2. Treatment of menaquinone-4 or menatetrenone can reduce the incidence of vertebral fracture for 50% but the effect to other non-vertebral fractures is not clear (23, 24).
3. In postmenopausal Asian women who take menatetrenone for 45mg daily with 1,500mg of calcium and vitamin D will maintain BMD level or increase lumbar spine BMD (25-27) and can also reduce the undercarboxylated osteocalcin significantly (25-28).

**Strontium ranelate**

1. An efficacy study of strontium ranelate (SR) found that treatment of strontium ranelate can reduce approximately 40-50% of the risks for spinal fracture for up to 3 years.
2. Another efficacy study also showed that treatment of strontium ranelate can reduce the risks of having non-vertebral fractures and hip fracture for 16% and 36% accordingly, as compared to placebo (30).
3. Integrated analysis of strontium ranelate (31) found that it can prevent the risk for new bone fractures in people of the age over 80 years for 32% and 31% for non-vertebral fractures. In addition, strontium ranelate also have potential to reduce the incidence of new bone fracture in patients with osteopenia for 30-50% (32).
Prescription of all previously described pharmacological treatment of osteoporosis, all bone formation stimulators, bone resorption inhibitors or mixed-action agents must be in combination with adequate intake of calcium and vitamin D (as suggested in part III-3). If patients are unable to intake enough level of calcium and vitamin D, supplemental of both should be given.

IV-3 Alternative therapy and non-pharmacological treatment

3.1 Hip protector

There are only few evidences supported the benefits of hip protector usage in prevention of hip fracture in a place other than a nursing home since the major problem is wearing compliance (33-35).

IV-4 Potential adverse events, prerequisites and contraindications in using anti-osteoporotic agents

4.1 Side effects, precautions and prohibitions in treatment of anti-osteoporotic agents

**Calcium** important side effects and precautions are;
- Having side effects of gastrointestinal tracts such as flatulence, constipated should be considered for stopping treatment.
- There were studies described that supplement of calcium increase the incidence for cardiovascular diseases such as ischemia, stroke and sudden death syndrome when compared to placebo (38), however, in other studies, no increased incidence for cardiovascular was observed (36, 37, 39).

**Vitamin D and vitamin D analogue** important side effects and precautions are;
- Few cases of increased level of blood calcium and urine calcium were found but only in a case which vitamin D was co-prescribed with high dosage of treatments and prescription of active forms of vitamin D such as calcitrol. Most of the studies did not found any significant increase in renal stones incidence.

**Hormone replacement therapy (estrogen and/or progestin)** important side effects and precautions are;
- Increasing risk for breast cancer in case of combined estrogen-progestin treatment (42, 43).
- Increasing risk for deep vein thrombosis in legs and lungs in the group with combined estrogen-progestin treatment more than estrogen alone (43, 44).
- Increasing risk for ischemic heart disease for the group that receive combined estrogen-progestin treatment and the risk will rise as the patients are older (43, 45).
- Increasing risk for stoke and in both combined estrogen-progestin treatment \(^{(43)}\) and estrogen alone \(^{(46)}\) in all ages \(^{(47)}\). Also both types of treatment affect cognitive function and may cause dementia \(^{(48-51)}\).

- Other side effects such as breast pain and abnormal vaginal bleeding.
  - Prescription of estrogen for osteoporotic treatment must be issued for patients without the risks of having breast cancer, uterus cancer, cardiovascular diseases, brain diseases and deep vein thrombosis. Moreover, mammogram should be assessed in patients annually.

**Biphosphonates** important side effects and precautions are;

- Side effects to GI tracts were observed with alendronate, risendronate and ibandronate administered orally. Mostly are mild cases of non-ulcer dyspepsia, gastro-esophagal acid reflux, nausea, vomiting and stomach ache. Side effects of i.v. ibandronate and zoledronate were less \(^{(52)}\).

- Some side effects to cardiovascular system were found such as increased arterial fibrillation in patients receiving bisphosphonate as compared to placebo receiving group, however, the evidence of the mechanism of side effect were not found therefore assessment of EKG prior to prescription is not necessary.

- Side effects to the bone system. Osteonecrosis of the jaws is mostly found in patient who already have cancer and the cancer metastasizes to the bone that receive bisphosphonate by injection. Nevertheless, there were reports in osteoporotic patients who received bisphosphonate also \(^{(53)}\) but were 100 times less frequent. However, teeth examination is not necessary before prescribing bisphosphonate.

- There were reports of atypical fractures in patients who received bisphosphonate for long term (average > 5 years) with the signature of low-energy trauma fracture with traverse configuration at subtrochanetric or at the shaft of femur with no clear cause \(^{(54, 55)}\). However the incident rate are minimal as compared to the global number of patients receiving bisphosphonate therefore, care should be take in cases that are on bisphosphonate treatment for longer than 5 years.

- Post-dose reactions are commonly found especially when bisphophonate is administered intravenously \(^{(56, 57)}\). Only few incidences of post-dose reaction were found with monthly dose, orally of bisphosphonate. Minor side effects that were found are fever, muscle pain, joint pain, flu-like symptoms which were only seen after the first dose but were ameliorated with in few days. These symptoms were rarely found with the following doses.

- There are 3 important criteria for administration of oral form bisphosphonates which are;
  a. Bisphosphonate must be taken when the stomach is empty, no foods in the stomach at all which is when after wake up in the morning. After
taking bisphosphonate for more than $\frac{1}{2}$ to 1 hour then the patients can have breakfast and other drugs.

b. Bisphosphonate must only be taken with water, no other types of fluid such as juices, soda, water with sweetener, milk, tea or coffee is allowed. Pills should not be grinded, chewed or broken into pieces in which the substances can be in direct contact to inside of the mouth since it can induce inflammation.

c. All normal activities can be done after taken bisphosphonate except lying for at least $\frac{1}{2}$ to 1 hour to prevent from the reflux since when bisphosphonate starts to diffuse, if it reenters the esophagus, it may cause esophagitis.

- Intravenous administration of bisphosphonate must be infused only and the time to totally infuse bisphosphonate must not exceed 15 minutes. I.V bisphosphonate must not be used in patient with renal problem which is indicated by GFR of $\geq 30$ml/min (creatinine clearance can also be used). This is because bisphosphonate is cleared only via renal. I.V. administration of bisphosphonate does not prohibit food intake or lying position after administration.

**Raloxifene** side effects and precautions

- It was found that treatment of raloxifene for longer than 2 years may increase the risk for having venous thromboembolism $^{(58, 59)}$. Therefore raloxifene should not be prescribed to patients who are already at risk of having venous thromboembolism. Other side effects are increase incidence of hot flashes $^{(59)}$ and leg muscle cramps $^{(60)}$.

**Strontium** side effects and precautions

- Strontium may cause minor effects such as liquid stool which should not be considered for treatment termination.
- There were also reports of increased risk for venous thromboembolism $^{(61)}$, the reason behind this side effect is not clear therefore strontium should not be used in patients who already are at risk of having venous thromboembolism.

**Teriparatide** side effects and precautions

- Blood calcium level and urine calcium level may slightly increase after starting the treatment but there was no report of renal stone incidence $^{(62)}$.
- Teriparatide may increase uric acid level in blood hence it should not be used in gout patients $^{(63, 64)}$.
- From studies in mouse model, mice that were administered for teriparatide for more than 20 months $^{(16, 65)}$ have higher incidence of osteosarcoma.
However, the dosage used for mice in this studies are 20 times more of what prescribed in human and the length of treatment is as long as the mouse lifespan (approximately 70-80% of mouse lifespan) hence, teriparatide can be used in human with careful consideration.

- Recent data showed that there were 2 incidences of osteosarcoma development in human after treatment of teriparatide \(^{(66, 67)}\). However, relative histories of teriparatide usage in these 2 patients are not clear since there were no information regarding the pre-diagnosis of cancer in these patients. In the second case, patient has undergone radiation therapy at the site where osteosarcoma developed \(^{(67)}\). Nevertheless, there are only 2 cases with side effect among over 500,000 people undergoing treatment with teriparatide which is less than the osteosarcoma incidence itself in people over 60 years old which is 1 in 250,000 cases \(^{(66)}\). Hence it is considered to be safe to use teriparatide for osteoporosis treatment in human \(^{(68)}\) but only with some prerequisites.

- Prerequisites for usage of teriparatide;
  a. Treatment should not be longer than 2 years
  b. Teriparatide should not be used in patient who have high risk of osteosarcoma such as
     - Having Paget’s disease
     - Have had radiation therapy at the bone
     - Have high level of alkaline phosphatase with no apparent cause.
     - In children whose epiphysis has not closed.
  c. Teriparatide is not recommended for use in patient with history of cancer within 5 years.
  d. Since teriparatide is an expensive drug and may cause serious side effects therefore these following tests should be done before prescription of teriparatide which are serum creatinine, serum calcium and intact PTH. All of these tests must turn out normal.

**Calcitonin** side effects and precautions

- Side effects of calcitonin are irritation of nasal lining and hot flashes \(^{(12, 69)}\).

**Menatetrenone** No major side effect has been reported for menatetrenone.

- However, menatetrenone must be carefully considered for use in patients who undergoing warfarin treatment since menatetrenone will inhibit warfarin effects \(^{(23, 70)}\).
IV-5 Monitoring treatment and duration of treatment

5.1 Follow-up and treatment evaluation

Treatment follow-up and evaluation for osteoporosis treatment should be considered in two angles which are effectiveness of treatment and adverse events of the treatment.

*Treatment effectiveness evaluation* can be divided into 2 categories

1. **Evaluation for drug response** is to assess whether the drug is effective in the individual or not. Since the goal for osteoporosis treatment is to reduce the risks for bone fracture but so far, there is no drug that can reduce the risk for bone fracture to zero (which is no bone fracture occurs). Hence, bone fracture that occurs during treatment cannot be inclined for ineffectiveness of the drug or no drug response in patients. To date, there are 2 ways to evaluate drug response which are;

1.1 **BMD assessment using axial DXA.** In principle, BMD should be increased or at least not decreased as compared to BMD before initiation of treatment. The period between the 2 assessments should be less than 1 year and the same axial DXA machine used for the first assessment before treatment must be also used for the second assessment. Axial DXA machine may have some imprecision however if lumbar spine BMD for before and after treatment reduces for $\geq 3\%$ yearly or total hip or femoral neck BMD reduces for $\geq 5\%$ annually (17, 18) after 1 year of treatment, this will considered as true reduction of BMD and probable inadequate response. Hence, if reduction of BMD is below these criteria then the drug can be judged as having response. On the other hand, if there is bone fracture occurred during treatment together with the decrease in BMD, this will mean that the patient has **inadequate response** to that particular drug and should be treated with other drug.

1.2 **Assessment using bone turnover markers (BTMs).** For drugs that inhibit bone resorption, bone resorption markers should be reduced after treatment. In contrast, if the drugs enhance bone formation, bone formation markers should be increase. Assessment should be done 2 times which are before the treatment and over 3 months after treatment. 30-40% increase in bone turnover marker must be met in order to be considered as effective. However, BTMs have high variation and are not convenient since patients must be NPO for at least 12 hours before blood drawn in the morning (between 7.00-9.00 am) and every blood drawn must be done at the same time of day.

2. **Evaluation for compliance and persistence of treatment.** Most problems of treatment concerning these 2 issues were usually found in orally administered drugs. Evaluation can be made by frequently asking patients of how and how often they take the treatment medicine every time they pay a visit. Also, patients should
also be asked if they take the medicine themselves or there is any person helping them for drug administration.

5.3 Period of treatment

The period of treatment has not yet been finalized because it is up to each particular drug that its conditions are different, also patient’s conditions and clinical trial results must be carefully considered. In general, treatment period should be long and continuous enough to reduce the risk for bone fraction to the satisfying level. Nevertheless, this may cause problems especially regarding the cost of treatment so, it is impossible to totally eliminate the risks for having bone fracture. Another issue to be considered is that there is not long-term information on a clinical study for anti-fracture efficacy because of the ethical reason. So, if patients take the medicine with good compliance and persistence, no fracture have been occurred during the treatment, patients have good drug response, BMD by axial DXA increase to the satisfying level, all risks for fracture can be managed and good exercise behavior and good nutrition, then the treatment can be stop for 5 years with continuous patient monitoring (drug holiday). However, during drug holiday, patients must be evaluated for risks and BMD or BTMs must be assessed every 1-2 years. Treatment should be re-started if the patients have new risks for bone fractures.
Table 4.1 Evidences and suggestions for osteoporosis treatment.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Benefit and Indication for use</th>
<th>Effect and remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate 10mg (ALN)</td>
<td>For prevention and treatment of osteoporosis. Indications for use (according to US-FDA) - For treatment of osteoporosis in postmenopausal women (postmenopausal osteoporosis, PMO). - For treatment of glucocorticoid-induced osteoporosis (GIO). - For treatment of male idiopathic osteoporosis (MIO).</td>
<td>- Reduce the risk for spinal fracture, hip fracture and other non-vertebral fractures (^{(71-74)}). - Administer orally once a day.</td>
</tr>
<tr>
<td>Alendronate once weekly 70mg (ALN-OW)</td>
<td>For prevention and treatment of osteoporosis. Same indications as ALN 10mg.</td>
<td>- Same as ALN 10mg (^{(75)}). - administer orally once a week.</td>
</tr>
<tr>
<td>Alendronate plus ALN 70mg + Cholecalciferol 2800IU (ALN-plus)</td>
<td>For prevention and treatment of osteoporosis. Same indications as ALN 10mg.</td>
<td>- Same as ALN 10mg (^{(75)}). - administer orally once a week. - Contains vitamin D3 2800 IU per week or 400 IU/day to reduce hypovitaminosis D and vitamin D deficiency (^{(76)}).</td>
</tr>
<tr>
<td>Risendronate 5mg (RIS)</td>
<td>For prevention and treatment of osteoporosis. Indications for use (according to US-FDA) - For treatment of osteoporosis in postmenopausal women (postmenopausal osteoporosis, PMO). - For treatment of glucocorticoid-induced osteoporosis (GIO). - For treatment of male idiopathic osteoporosis (MIO).</td>
<td>- Reduce the risk for spinal fracture, hip fracture and other non-vertebral fractures (^{(77, 78)}). - Administer orally once a day.</td>
</tr>
<tr>
<td>Risendronate once weekly 35mg (RIS-OW)</td>
<td>For prevention and treatment of osteoporosis. Same indications as RIS 5mg.</td>
<td>- Same as RIS 5mg (^{(79)}). - administer orally once weekly.</td>
</tr>
<tr>
<td>Ibandronate once</td>
<td>For prevention and treatment of osteoporosis.</td>
<td>- Reduce the risk for</td>
</tr>
<tr>
<td>Regimen</td>
<td>Benefit and Indication for use</td>
<td>Effect and remark</td>
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</tbody>
</table>
| monthly 150 mg (IBN-OM)       | osteoporosis. Same indications as ALN 10mg                                                    | spinal fracture[^80, 81], hip fracture and other non-vertebral fractures[^82].  
- Administer orally once monthly. |
| Zoledronate infusion          | For prevention and treatment of osteoporosis. Indications for use (according to US-FDA)      | Reduce the risk for spinal fracture[^56, 57], hip fracture and other non-vertebral fractures.  
- Infuse intravenously every year. |
| Every 1 year 5mg (ZOL)        | - For treatment of osteoporosis in postmenopausal women (postmenopausal osteoporosis, PMO).   |                                                                                                                                                   |
|                               | - For treatment of glucocorticoid-induced osteoporosis (GIO).                                 |                                                                                                                                                   |

* Use of Ibandronate for reduction of vertebral fracture is studied by RCTs but all data for Ibandronate usage for reduction of other non-vertebral fractures are from synthesis data and pooled analysis from RCTs.
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Benefit and Indication for use</th>
<th>Effect and remark</th>
</tr>
</thead>
</table>
| Estrogen                   | For prevention and treatment of osteoporosis. Indications for use (according to US-FDA)  
                          - For treatment of osteoporosis in postmenopausal women (postmenopausal osteoporosis, PMO).                                                                                                                    | - Reduce the risk for spinal fracture \(^{(6, 7, 8)}\) and hip fracture.  
                          - Administer orally once a day (other preparation such as dermal patch has no data for efficacy).                                                                                                                           |
| Raloxifene (RLX) 60mg      | For prevention and treatment of osteoporosis. Indications for use (according to US-FDA)  
                          - For treatment of osteoporosis in postmenopausal women (postmenopausal osteoporosis, PMO).                                                                                                                    | - Reduce the risk for spinal fracture \(^{(9, 83)}\).  
                          - Administer orally once a day.                                                                                                                                                                                                 |
| Calcitonin Nasal spray 200IU/puff | For prevention and treatment of osteoporosis. Indications for use (according to US-FDA)  
                          - For treatment of osteoporosis in postmenopausal women (postmenopausal osteoporosis, PMO).                                                                                                                    | - Reduce the risk for spinal fracture \(^{(12)}\).  
                          - Use for pain reduction from osteoporosis spinal fracture \(^{(13)}\) (not exceeding 8 weeks)  
                          - Puff into nose every day.                                                                                                                                                                                                       |
| Menatetrenone (MK-4) 15mg  | For treatment of osteoporosis. Indications for use (according to Japan-FDA)  
                          - For treatment of osteoporosis in postmenopausal women (postmenopausal osteoporosis, PMO).                                                                                                                    | - Reduce the risk for spinal fracture \(^{(12)}\).  
                          - Administer orally 3 times a day (45mg/day).                                                                                                                                                                                                                                                |

** For estrogen, the evidence for reduction of risks for vertebral fracture and other non-vertebral fractures was reported by WHI which use conjugated equine estrogen which dose not extend to the use of estrogen by other preparations.
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Benefit and Indication for use</th>
<th>Effect and remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strontium renelate</td>
<td>For treatment of osteoporosis. Indications for use (according to EMEA)</td>
<td>- Reduce the risk for spinal fracture $^{(14, 15)}$ and other non-vertebral fractures.</td>
</tr>
<tr>
<td>2g/sachet</td>
<td>- For treatment of osteoporosis in postmenopausal women (postmenopausal osteoporosis, PMO).</td>
<td>- Administer orally once a day.</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>For treatment of osteoporosis. Indications for use (according to US-FDA)</td>
<td>- Reduce the risk for spinal fracture, hip fracture and other non-vertebral fractures $^{(14, 15)}$.</td>
</tr>
<tr>
<td>20µg/inject</td>
<td>- For treatment of osteoporosis in postmenopausal women (postmenopausal osteoporosis, PMO).</td>
<td>- Injection intradermally every day.</td>
</tr>
<tr>
<td></td>
<td>- For treatment of glucocorticoid-induced osteoporosis (GIO).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- For treatment of male idiopathic osteoporosis (MIO).</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>Recommended for all osteoporosis patients in case that patient may not receive enough calcium from food intake (84)</td>
<td>Only calcium intake will not protect from bone resorption or bone fracture.</td>
</tr>
<tr>
<td>Less than 1,200mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Elemental calcium)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen</td>
<td>Benefit and Indication for use</td>
<td>Effect and remark</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Vitamin D 400-800 IU/day</td>
<td>Recommended for all patients with co-supplement of calcium and co-treatment to other drugs except in patients who already receive vitamin D derivatives.</td>
<td>Prescription together with calcium may help reduce bone resorption.</td>
</tr>
<tr>
<td>Vitamin D derivatives</td>
<td>For treatment of glucocorticoid-induced osteoporosis (GIO) (86, 87). Use with the lowest dosage together with calcium and other osteoporotic drugs in case the normal vitamin D cannot be found or in case of very old patients (over 65 years old)</td>
<td>- When co-prescribed with calcium will help maintain or slightly increase BMD (85).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Be cautious for development of hypercalcemia and hypercalciuria (88).</td>
</tr>
</tbody>
</table>
### Reference


84 Richy F, Schacht E, Bruyere 0, Ethgen 0, Gourlay M, Reginster JY. Vitamin D analogs versus native vitamin D in preventing bone loss and osteoporosis-related fractures: a comparative meta-analysis. Calcif Tissue Int 2005;76(3) 176-86.


88 Ringe JD, Schacht E. Potential of alfacalcidol for reducing increased risk of falls and fractures. Rheumatol Int 2009;29(10)1 177-85.
V Glucocorticoid-induced osteoporosis (GIO)

V-1 Introduction and epidemiology

1.1 Introduction

Because of anti-inflammatory and immunosuppressive properties, glucocorticoids is widely used to treat diseases in many system such as dermal, respiratory, renal, arthritis and rheumatism, etc. Glucocorticoids, however, can cause several side effects such as hyperglycemia, cataract and osteoporosis etc. It also primarily causes secondary osteoporosis. There is a study showing that risk of non-vertebral, hip and vertebral fractures are increased of 1.33, 1.61 and 2.6 times, respectively. The risk is increased by the dosage in used, and it can be decreased immediately after stop using glucocorticoids.\(^{(1,2)}\)

1.2 Epidemiology

There is a study showing that about 1-3% of people age 50 and older experienced of using glucocorticoids.\(^{(3)}\) A study in England in patients age 55 and older showed that about 1 of 70 individuals (about 1.4%) had continuously used glucocorticoids for at least 3 years with average of 3 years \(^{(4)}\)

Bone mass is rapidly decrease within 6-12 months after start using glucocorticoids, and the more dosage is used, the faster loss of bone mass is occurred.\(^{(5)}\) Loss of bone mass is occurred on vertebral and hip bones most including trabecular bones. At the first year, rate of bone mass loss is about 5% and became 1-2% in the next years.\(^{(6,7)}\) Moreover, it is found that loss of bone mass is more related to cumulative dose than daily dose of glucocorticoids.

V-2 Pathophysiology and risk assessment

2.1 Pathophysiology

Pathophysiology of glucocorticoid-induced osteoporosis (GIO) is complicated because it relates to many factors including dose, cumulative does and treatment period and all of these factors resulting in GIO.\(^{(8-9)}\) In addition, bone fracture occures in these patients at the same bone density. Individual taking glucocorticoid has higher risk of osteoporosis than one with only menopause.\(^{(10-11)}\) Therefore, patients should be protected and treated immediately after taking glucocorticoid. Moreover, diseases such as rheumatic arthritis and ankylosing spondylitis requiring glucocorticoid, also cause osteoporosis themselves.\(^{(8)}\) Other factors including age, gender, menopause, and bone mass before taking glucocorticoid also relate to osteoporosis\(^{(12)}\)

Glucocorticoid activities causing osteoporosis by reducing bone formation, increasing bone resorption\(^{(13)}\) causing secondary hyperparathyroidism\(^{(14)}\), reducing calcium absorption of intestine\(^{(15)}\) and increasing urine calcium excretion,\(^{(16)}\) suppressing action of osteoblast combining with increasing apoptosis of osteoblast
and osteoclast; increasing receptor activator of NF-KB ligand (RANKL), decreasing of osteoprotegerin (OPG) suppressing action of hypothalamic pituitary gonad axis causing reduction of estrogen, testosterone and adrenal androgen effecting bone formation. All of these results in osteoporosis.

2.2 Risk factors

Currently, risk assessment of glucocorticoid-induced osteoporosis, as well as post-menopausal osteoporosis, can be assessed with risk factors of recent bone fractures including aging (65 or older), menopause, low body mass index and risk diseases to osteoporosis (e.g. rheumatoid arthritis), chronic lung disease, organ transplantation, combined with assessment of bone density measurement when taking drug. As mentioned, patients taking glucocorticoid have possibility of bone fracture with higher bone density, and risk is increasing while T Score below -1.0. Their bone density can be rapidly decrease with decreasing rate about 10% or 1 standard deviation (SD) at the first year. Therefore, many countries’ guideline suggests that T Score below -1.0 is an indicator for patient to have treatment against glucocorticoid effects.

V-3 Diagnosis

Diagnosis of glucocorticoid-induced osteoporosis is as well as in common osteoporosis, but based on glucocorticoid use history and combined with BMD T-score below -2.5 and SD for L-spine, femoral neck or total hip.

V-4 Prevention and treatment

4.1 Methods for the prevention and treatment of glucocorticoid-induced osteoporosis.

Prevention and treatment of glucocorticoid-induced osteoporosis is similar to post-menopausal osteoporosis, but with following addition.

1. General practices should be use in all patients
   1.1 Using minimum dose of glucocorticoids in minimum period with particular use and as low as possible to control main disease.
   1.2 Regularly exercise
   1.3 Decreasing or quitting smoking and drinking
   1.4 Prevention of falls
   1.5 Taking sufficient of calcium, at least 1,200 mg. of elemental calcium
   1.6 Taking Vitamin D for 800 IU a day

2. Treatment is used when expect to take glucocorticoids as equal dose to 7.5 mg of prednisolone for above 3 months, having risk factors or BMD T score is lower than -1.0.
Most drug treatments can be used as in Table 4.1 (in unit IV)

2.1. First choices of drug treatments\(^{(27-29)}\)
   2.1.1. Alendronate
   2.1.2. Risedronate
   2.1.3. Zoledronate

2.2. Second choices of drug treatments (in case that the first group is not effective)\(^{(27,28)}\)
   2.2.1. Vitamin D derivative such as alphacalcidol and calcitriol
   2.2.2. Sex hormones
       2.2.2.1. Estrogen replacement therapy in premature menopause
       2.2.2.2. Testosterone replacement therapy in men with low testosterone
   2.2.3. Teriparatide is particularly used in patient with high risk,\(^{(30)}\) history of osteoporotic fracture at many position or at joint, and in case that patients do not respond to bisphosphonates, and it should be used as in IV-2 2.2 (Teriparatide, TPTD)

2.3. There is no enough evidence for using SERMs, calcitonin, menatetrenone and strontium ranelate as the treatments of glucocorticoid-induced osteoporosis.

V-5 Monitoring treatment

5.1 Monitoring treatment

1. As glucocorticoid-induced osteoporosis has high rate of losing bone mass, patients experienced using glucocorticoid is suggested to have bone mass check every 6-12 months. In case patients with none experience of treating with bisphosphonates take glucocorticoid, they should be re-checked in a year. In case that patient does not respond for treatment, patient should consult with therapist
2. For treatment period, patients taken glucocorticoids should be treated with drug until they stop using glucocorticoids\(^{(31)}\)
Reference


VI  Osteoporosis in men

VI-1 Introduction and epidemiology

1.1 Introduction and definition

**Definition**

Osteoporosis in men is a disease causing decreasing of bone mass and irregularity in bone structure resulting in fragile bone in men.

**Introduction**

Osteoporosis occurs in women more than men because young men have higher level of bone mass and decreasing of bone mass in men is slower. Therefore, physicians most focus on osteoporosis treatment for post-menopausal women and old women. However, epidemiology studies found that 30% of hip fracture and 20% of vertebral fracture had occurred in men.\(^1\) It is expected that in 2025, the number of men with hip fracture will be as much as the number of women recently having hip fracture \(^1,2\). In addition, it is found that men with hip and vertebral fractures has higher mortality and incurrent diseases.\(^3,4\) In consequence, osteoporosis in men is one of important public health problem and it is becoming more important because people live longer, and ratio of old people in Thailand is much more increasing.

1.2 Epidemiology

The data shows that one third of hip fractures have occurred in men, and because of increasing of old people, it is expected that in 2050 patients with hip fractures throughout the world will extremely increase from 0.5 to 1.8 millions.\(^1,4\) From the US observation found that 6% of men age above 50 have hip fractures and 5% of those men have vertebral fracture and one eighth of those fractures are associated with osteoporosis.\(^5\)

Because men have higher level of bone mass, osteoporotic fracture in men is about 5-10 years late — in women the incidences for bone fractures increase from the age of 65 while in men the incidences start to rise during the age of 75. In addition, it is found that men have bigger bone, and loss of bone mass slower occurs because hormones in men do not rapidly change as in women.

According to several studies, vertebral fractures in Asian countries are lower than those in western.\(^8-16\) Data of Thailand from Asian Osteoporosis Study (AOS) shows that in 100,000 of people, there are 144 men and 289 women with hip fractures. The incident of vertebral and wrist fracture in Thailand have not been studied.
Osteoporosis distribution in Thai men includes 12.6% of hip bone, 4.6% of vertebral bone and 3.9% of both position.\(^{(17)}\)

### 1.3 Risk factors

Currently, risk assessment of osteoporosis in men, as well as post-menopausal osteoporosis (most risk factors are the same), can be assessed with risk factors of recent bone fractures including risk factors of bone mass loss. The risk factors are divided into:

- Non-modifiable risk factors of bone mass loss including age and genetic\(^{(18-19)}\)
- Modifiable risk factors including smoking,\(^{(21-24)}\) low physical inactivity,\(^{(20,25,26)}\) low body mass index,\(^{(21,22,25)}\) excess alcohol consumption,\(^{(27,28)}\) Vitamin D deficiency,\(^{(22,30)}\) low protein,\(^{(31)}\) taking some drugs resulting in loss of bone mass such as steroid, antiepileptic,\(^{(22)}\) thiazolidinedione,\(^{(33)}\) and class SSRI of antidepressant.\(^{(34)}\)

### VI-2 Assessment and diagnosis

#### 2.1 Diagnosis

Osteoporosis in men can be diagnosed by measurement of bone mineral density (BMD) commonly on L-spine area of vertebral and hip bone. Osteoporosis in men age 50 and older can be diagnosed by comparing with standard deviation of bone density of men age 30-35 in similar races. It is considered as osteoporosis when T-score is -2.5 or less.\(^{(35,36)}\)

Osteoporosis in men age 50 and younger should be diagnosed by comparing with standard deviation of bone density of men in the same age in similar races (A-score) more than using T-score\(^{(36)}\)

#### 2.2 Check up and special diagnosis

Osteoporosis in men differs from post-menopausal osteoporosis as the causes of second osteoporosis can be found in about a half of patient, in other words, we can find the causes of osteoporosis. The assessment includes nursing history, checkup and laboratory investigation.

*Nursing history*

To assess risk factors of osteoporosis, nurse history is performed including symptoms of diseases associated with secondary osteoporosis and risk of hip fracture including imbalance and falling easily, and history of bone fracture.
**Checkup**

To check bone fracture, checkup is performed including measurement of height and weight, observation of patients’ walking style and balancing, and general bone checkup including vertebral column. Decreasing in height, having kyphosis or kyphoscoliosis indicate that patients have vertebral fracture. Cushingoid habits, thyroid grand and thyrotoxicosis should also be checked.

**Laboratory investigation**

*First level: preliminary laboratory investigation (All patients should be checked for causes of osteoporosis)*

1. Complete blood count
2. Serum calcium, phosphorus
3. Serum albumin
4. Serum alkaline phosphatase
5. Serum creatinine and liver transaminases
6. Thyroid stimulating hormone (TSH)
7. Testosterone

*Second level: additional checkup, in case that the first check is not effective (not important to check in all patients)*

1. Serum protein electrophoresis
2. Parathyroid hormone
3. Serum 25-hydroxy vitamin D
4. 24-hour urine calcium
5. 24-hour urine free cortisol

**Who should be checked for bone density?**

Indicator for BMD measurement in men\(^{36}\):
1. Having hypogonadism
2. Experience of bone fraction without intense crash
3. Having malabsorption
4. Primary hyperparathyroidism
5. Going to be or being treated with glucocorticoids
6. Being treated with organ transplantation
7. Having thin bone
VI-3 Prevention

3.1 Prevention of osteoporosis in men\(^{(37-39)}\)

- Should not consume alcohol regularly and not over 3 standard units a day: 2 ounces for alcohol, 7 ounces for wine and 18 ounces for beer \(^{(40)}\)
- Stop smoking
- Regularly exercise especially weight bearing exercises such as walking or running.
- Older people should use balanced exercise to increase strength of muscle and balancing and decrease falling.
- Consume sufficient calcium from foods and/or supplemental calcium, over 800 mg a day (elemental calcium)
- Take supplemental vitamin D for about 400-800 IU a day, or expose to the sun about 10 minutes a day
- Enlightened and suggested in using drugs causing loss of bone mass such as anti-epileptic, glucocorticoid, anti blood clotting, thyroid hormone and anti male hormone, etc.
- Enlightened about factors and diseases causing loss of bone mass and may causing osteoporosis for correct prevention

VI-4 Treatment and follow-up

4.1 Methods for treating osteoporosis in men

According to studies about drugs treating osteoporosis in men, most drugs can be use as in table 4.1 (unit IV) but the first choice should be bisphosphonates including alendronate\(^{(41)}\) or risedronate\(^{(42)}\) or zoledronic acid\(^{(43)}\) because they are certified for treating osteoporosis in men, and patients must also take sufficient calcium. Moreover, testosterone replacement therapy may be performed in case that patients have low level of testosterone. Treatment with these drugs can effectively treat patients with glucocorticoid-induced osteoporosis, androgen-deprived therapy, osteogenesis imperfect, post-transplantation and stroke.

Other group of drugs studied is parathyroid hormone (teriparatide\(^{(44-47)}\) resulting in reduction of vertebral fracture, but with limitation of expensive cost, only injection type available and not appropriate to be used with potent antiresorptive drugs,\(^{(48)}\) so it should be use as the second choice and only in patient with high risk — patient experiencing in bone fracture in many positions or hip fracture and in case that patients do not response to bisphophonates. However, the same indicators in IV-2 2.2 (Teriparatide, TPTD) are used.

There are not enough evidences for SERMs grups, calcitonin, menatetrenone and strontium renelate, to be used as treatment for osteoporosis in men.
4.2 Monitoring treatment

Monitoring methods$^{(37,38)}$

1. Monitoring symptoms and signs of osteoporosis and bone fracture
2. Bewaring and monitoring of incurrent diseases
3. Patient with low male hormones and treated by replacement hormones including testosterone or androgen, should be checked up and had following laboratory investment:
   - Always check for blood pressure
   - Rectum check for assessment of irregularity of prostate gland
   - 6-12 monthly check for blood concentration level and lipid level including total cholesterol, triglyceride, HDL-C and LDL-C
   - Annual check of prostate-specific antigen (PSA) level (in patients age 65 and older)
4. Suggestions for monitoring after treatment

   - Patient with T-score below -2.5 and having drug therapy should be assessed for density of lumbar, vertebra and hipbone after 1-2 years of treatment
   - Patient with T-score between -2.5 to -1 and taking many risks of osteoporosis should be checked for density of lumbar, vertebra and hipbone after 1-2 years of treatment
   - Patient with T-score above -1 does not need to be checked bone density in 5 years except in case having additional clinical risk

Because bone mass changes slowly, BMD monitoring should not be performed for 1 year. Although coefficient of variation (CV) of DXA method is low, detection is available for more changes which are over machine ability.$^{(49)}$
Reference


29. Lamberg-Allardt CJ, Outila TA, Kärkkainen MU, Rita HJ, Vaista LM. Vitamin D deficiency and bone health in healthy adults in Finland: could this be a concern in other parts of Europe? J Bone Miner Res 2001;16(11):2066-73.


