Perspective

Osteoporosis: Overview in Disease, Epidemiology, Treatment and Health Economy

Chatlert Pongchaiyakul MD*,
Thawee Songpattanasilp MD**, Nimit Taechakraichana MD***

** Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen*
*** Department of Orthopaedic, Phramongkutklao College of Medicine, Phramongkutklao Hospital, Bangkok*
**** Menopausal Research Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok*

J Med Assoc Thai 2008; 91 (4): 581-94
Full text. e-Journal: *http://www.medassocthai.org/journal*

Disease Overview

Osteoporosis is a disease characterized by low bone mass and micro-architectural deterioration of the bone tissue, leading to bone fragility and increased risk of fracture, particularly of the spine, wrist, hip, pelvis and upper arm.

Osteoporotic fractures are associated with significant reductions in quality of life due to disability, pain, and deformity; as well, they constitute an important cause of death among the elderly and impose a considerable economic burden on health services worldwide[1]. The high prevalence of osteoporosis coupled with its significant health consequences makes effective prevention and treatment a leading concern for heath care practitioners.

Disease Definitions

In 1993, a conference was held in which an internationally agreed upon definition of osteoporosis was developed. Osteoporosis was defined as "a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of the bone tissue with a resultant increase in fragility and risk of fracture"[2]. Recently the United States National Institute of Health has defined osteoporosis as follows: "a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality"[3].

In 1994, the World Health Organization (WHO) classified patients according to bone mineral density (BMD) values and published the information. The intended use for the classification was to allow for the comparison of prevalence estimates globally. However, in the absence of methods of measuring bone quality, the diagnosis of osteoporosis tends to be made on the basis of BMD using the following WHO classification[4,5]:

Normal BMD is defined as a T-score above -1.0 standard deviation (SD) compared with young adult mean.

Osteopenia (low BMD) is associated with a T-score between -1.0 and -2.5 SD inclusive. Osteopenia is also a term used by radiologists to indicate that the bones on a plain x-ray film appear to be of decreased mineral content.

Osteoporosis is defined as a T-score lower than -2.5.SD compared with young adult mean.

Severe Osteoporosis describes patients whose T-score is below -2.5 SD and have suffered a fragility fracture.

However, low BMD alone does not account for all fracture risk in osteoporotic patients. As a result other major risk factors are commonly considered when making treatment decisions[5].

Correspondence to: Pongchaiyakul C, Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand. Phone: 043-363-664, Fax: 043-347-542, Email: pchatl @kku.ac.th

Disease Prevalence

In the United States, the National Health and Nutrition Survey (NHANES III) estimated that 13% to 18% of women have osteoporosis and 27% to 50% have osteopenia.[6] The risk of osteoporosis rises with age, evidenced by the finding that approximately 70% of 80-year-old women in the United States have postmenopausal osteoporosis[6].

BMD measurements can be taken at a number of sites including the femoral neck, the lumbar spine, and distal forearm. In considering osteoporosis of the hip alone it is estimated that 7.8 million women in the United States are currently affected. This figure is expected to rise to 10.5 million by 2020, primarily due to the aging population[7]. In the United States, the number of persons aged 65 years and over is expected to increase from 32 to 69 million between 1990 and 2050[8]. The number of persons aged 85 and older is expected to rise from 3 million in 1990 to 15 million in 2050[7].

The same demographic changes are also predicted globally with the number of persons aged 65 and older expected to rise from 323 million in 1990 to 1555 million by 2050[8]. This could cause the number of hip fractures globally to increase from 1.7 million (1990) to an estimated 6.3 million in 2050[9]. If fracture incidence rates simultaneously increase worldwide by 1% annually, the projected number of hip fractures would be 8.2 million by 2050[10]. If rates were stable in North America and Europe, but increase in developing countries by 3% annually, the total number of hip fractures globally would surpass 21 million by 2050[10].

Disease Incidence

Fractures represent the main clinical manifestation of osteoporosis. Commonly occurring fractures include vertebral fractures, fractures of the distal radius and hip fractures. For Caucasian women living in North America, the lifetime risk of fractures at age 50 is 17.5%, 15.6%, and16%, for the hip, spine and forearm respectively[11]. This translates into a lifetime risk of 40% for any fragility fracture[11]. Similar rates have been reported from parts of Europe, however there is a marked variation in fracture risk between countries, regions, and within countries[12].

Hip Fractures

Of the approximately 1.7 million hip fractures that occur globally each year the majority are the result of a fall from the standing position. Worldwide hip fracture incidence rates increase with age. Hip fracture rates are highest in Caucasian women living in temperate climates, are somewhat lower in women from Mediterranean and Asian countries and are the lowest in women living in Africa[13-15]. This despite the fact that hip fracture incidence rates have been increasing with the urbanization of central parts of Africa. Other countries in economic transition, such as the Hong Kong Special Administration Region (SAR) of China, have also seen significant increases in age-adjusted fracture rates in recent decades[16,17]. Conversely, rates in industrialized countries appear to have plateaued[16-18].

Among Caucasians the ratio of hip fractures for females to males is approximately 2:1. This trend is not seen in Blacks or Asians where the ratio between males and females approaches unity[12].

Although hip fractures account for only 4.7% of all osteoporotic fractures among women aged 50-55 years and 33.3% of osteoporotic fracture for women aged 85-89 years, the event receives the most attention presumably because of their high cost to individuals and to healthcare payers[19]. The average hospital admission for a hip fracture in Europe is 20-30 days[20]. In addition, hip fractures are associated with significant mortality. Of all the patients, 15-30% will die within six months of experiencing a hip fracture[21,22]. Patients who survive hip fracture experience significant disability, which results in the need for long-term care in approximately 20%[23]. In industrialized countries longterm care occurs at the institutional level. Conversely, in developing countries the majority of patients return home to receive long-term care.

Vertebral Fractures

Less than 50% of all vertebral fractures come to clinical attention and only 1/3 to 1/5 of clinically symptomatic fracture require hospitalization[24,25]. Thus, unlike hip fractures, which all come to clinical attention, it is difficult to estimate the incidence of vertebral fractures[25], although it is generally estimated that the rates are roughly twice that of hip fracture incidence rates. The incidence of vertebral fracture increases with increasing age and the female to male ratio is approximately 2:1. Vertebral fractures are most common among Caucasian and Japanese women and are less common among Black women[24].

Vertebral fractures are believed to be important predictors for future osteoporotic fractures[26,27]. It is estimated that 20-26% of postmenopausal women will experience a new vertebral and/or non-vertebral fracture (i.e. hip, forearm/wrist, other) within 1 year of an incident vertebral fracture[26,27] and this risk increases

with the number of prevalent vertebral fractures[26]. This "fracture cascade" results in pain, kyphosis, loss of height, disability, and increased mortality among osteoporotic patients[28-30]. Patients hospitalized for a vertebral fracture spend approximately 6-30 days in hospital[31,32].

Disease Pathophysiology

Bone serves as a support structure to allow movement, and protection of various organs and attachment of muscles[33]. It also, provides a storage bank of inorganic elements for mineral homeostasis and blood-producing cells[33].

Bone is not completely solid; it includes spaces, which act as channels for blood vessels to supply bone cells with nutrients. The overall architecture of the bone is divided into trabecular bone and cortical bone. Cortical bone, which forms a compact shell around the more delicate trabecular bone, accounts for about 75% of the skeleton. Trabecular bone, which is formed by an interconnecting latticework of bone, accounts for the remaining 25% of the skeleton[33].

Bone Remodeling

There are four major types of cells within the bone, each with a distinct function: osteoblasts, osteoclasts, osteocytes, and lining cells.

Osteoblasts are primarily responsible for bone formation, which increases bone mass. Osteoblasts form a contiguous layer of cells that, in their active state, are cuboid in shape[34]. During bone formation, osteoblasts synthesize and secrete a collagen based organic matrix for new bone. The life span of a team of osteoblasts at a particular site ranges from three months to 1.5 years[34]. As formation progresses, the number of osteoblasts decrease at the site and the cells become flattened. Eventually, osteoblasts become incorporated into bone as osteocytes, which are no longer involved in bone building or remain on the surface as lining cells, which are thought to regulate calcium and phosphate movement into and out of the bone[34]. Osteoblast activity occurs continuously in all living bone; therefore some new bone is constantly being formed.

Osteoclasts are primarily responsible for bone resorption, a physiological process that results in the loss of bone[34]. Osteoclasts have a discoid shape with a ruffled border and are located on trabecular bone and in cortical bone. In trabecular bone, osteoclasts are located on the surface, in shallow pits called lacuna. In cortical bone, osteoclasts are located in cylindrical tunnels. In either bone type, the life span of an osteoclast is approximately seven weeks[34].

During infancy and childhood osteoblasts are usually more active than osteoclasts; the net effect being an increase in bone mass. This process is called modeling and is responsible for shaping or sculpting the skeleton during growth. Modeling slows during adolescence and stops completely by the mid twenties[35]. At this point, remodeling activities, wherein old bone is continually resorbed and new bone is formed in its place, increase. The net effect of remodeling, is either no change or net loss in bone mass. As a person ages, repeated strain or stress on bone from ordinary mechanical use results in the development of microdamage and a reduction in the strength of the bone[35]. Consequently, remodeling is necessary to repair the damage and any reduction in the rate of remodeling may increase the risk of spontaneous fracture[35].

Bone Loss Leads to Osteoporosis

Osteoporosis occurs when there is an imbalance between bone resorption and bone formation. In persons with osteoporosis, bone resorption takes place to a greater extent than bone formation, resulting in a net loss in bone mass. Bone loss can occur in several ways[36]: 1) Osteoclasts may create an excessively deep cavity, which cannot be filled by the action of the osteoblasts. 2) The function of the osteoblasts may be diminished, such that even a normal sized lacuna is not filled. 3) An increased number of osteoclasts can be activated which, when in combination with either of the above two processes, may result in increased bone loss.

Patterns of Age-Related Bone Loss

Bone mass increases progressively during growth until skeletal maturity. At skeletal maturity men have a 10-15% greater bone mass than women[36]. This difference partially explains the higher fracture rate in women. Another factor is the accelerated period of bone loss at menopause, which is thought to be caused by a reduction in the production of estrogen. The exact mechanism of estrogen action is unknown, however high affinity receptors have been located on both osteoclasts and osteoblasts[36]. Bone loss is most rapid during the first 5 to 8 years after menopause, with an annual loss of BMD of 3% to 5%. Bone loss continues thereafter, but at a slower rate of 1 to 2% per year[37]. Trabecular bone, which has a high annual metabolic turnover rate (about 25% vs. 3% for cortical bone), is most greatly affected by osteoporosis. The lumbar spine

and femoral trochanter are sites that have a significant trabecular composition, and are particularly susceptible to osteoporosis and ultimately fractures.

Risk Factors

BMD is not the only factor that has been suggested by the WHO and other organizations as a predictor of the risk of future fractures. Age is also an important factor that may affect bone density and absolute risk of fracture. Relative to women aged 50-54, the odds of having osteoporosis were 5.9 fold higher in women aged 65-69 and 14.3 fold higher in women aged 75-79 in a study of over 200,000 postmenopausal women[38]. In elderly women with no history of fracture, variables such as low calcium intake, low vitamin D intake, and history of fracture in 1st degree relatives, were identified as risk factors for hip fracture in 4-year prospective study[39]. The presence of a vertebral fracture is a strong risk factor; increasing the risk of an additional vertebral fracture by 5-fold.

Other factors found in some studies include premature menopause, chronic therapy with oral corticosteroids, high caffeine intake, Caucasian or Asian ethnicity, lean body build, low levels of physical activity, smoking and excessive alcohol use[40].

The National Osteoporosis Foundation (NOF) classifies risk factors as non-modifiable and modifiable[41].

Non-modifiable:

Personal history of fracture as an adult
History of fracture in first-degree relatives
Caucasian race
Advanced age
Female sex
Dementia
Poor health/frailty

Modifiable:

Current cigarette smoking
Low body weight/thinness (< 127 lbs)
Estrogen deficiency
Early menopause (< aged 45) or bilateral ovariectomy
Prolonged premenopausal amenorrhea (> 1 year)
Low calcium intake (lifelong)
Alcoholism
Impaired eyesight despite adequate correction
Recurrent falls
Inadequate physical activity
Poor health/fragility

Currently, there is no universally accepted policy of screening to identify patients with osteoporosis, nor is it clear whether it is appropriate to screen asymptomatic postmenopausal women. Most organizations that endorse guidelines recommend using risk factors to select patients for bone density testing, but lack of evidence prevents consensus on what risk factors to use. The Osteoporosis Society of Canada (OSC) recommends that all postmenopausal women over 50 years of age be assessed for the presence of risk factors related to osteoporosis. The four key factors chosen by the OSC are low BMD, prior fragility fracture, age and family history of osteoporosis. The U.S. Preventative Services Task Force recommends that women 65 years and older should be screened routinely for osteoporosis. Routine screening should begin for women aged under 65, who are at increased risk for fractures related to osteoporosis. In 1998, the NOF in collaboration with several professional organizations issued screening guidelines recommending bone density testing for all women 65years and older. Some of the collaborating groups included the American Academy of Orthopedic Surgeons, the American College of Rheumatology and the American Society of Bone Mineral Research recommended the testing was also screened for younger postmenopausal women who have had a fracture or who have one or more risk factors for osteoporosis[42].

Available Drug Treatments

The purpose of drug therapy among osteoporotic patients is to reduce the risk of fracture, stabilize or achieve an increase in bone mass, relieve symptoms of fractures and skeletal deformity, and maximize physical function[43]. Although there have been many agents have been used for treatment in postmenopausal women with the incidence of vertebral and non-vertebral fractures as primary endpoints. Results of these trials have shown that several agents reduce the risk of fracture by as much as 30-50%.

Calcium and Vitamin D

Calcium is an important nutrient in the prevention and treatment of osteoporosis as it slows the rate of bone loss, especially in elderly women and in those with a low calcium intake. Vitamin D, obtained either from food or synthesis in the skin during sunlight exposure, is also given as a supplemental treatment for osteoporosis. Calcium and vitamin D are often taken as an adjunct to other therapies for osteoporosis. Controlled clinical trials have demonstrated that these agents can reduce the risk of fracture. In a French study of 3,270 elderly women treated for 3 years with

calcium (1,200 mg daily) and vitamin D (800 IU daily), the probability of hip and all non-vertebral fractures was significantly reduced by 29% and 24% respectively, compared to placebo[44,45].

Bisphosphonates

Bisphosphonates are stable analogues of naturally occurring pyrophosphate[46]. Clinical trials of bisphosphonates consistently provide solid evidence of efficacy in preventing both vertebral and non-vertebral fractures. The availability of the different bisphosphonates varies across countries, however etidronate, alendronate, and risedronate seem to be most commonly used.

Etidronate was the first bisphosphonate developed. The agent is administered intermittently, typically at 400 mg per day for 2 weeks and then repeated every 3 months[40]. Findings of a meta-analysis suggested relative risk reduction of 37% (95% CI 8% to 56%) for vertebral fractures, but no significant effect was noted for non-vertebral fractures[47].

Alendronate is given continuously at a daily dose of 5 mg for prevention of osteoporosis and 10 mg for treatment of established osteoporosis[43]. Results from a study[48] of 2,027 osteoporotic women with at least one prevalent vertebral fracture who were treated with 5 mg alendronate for the first two years and 10 mg of alendronate during the subsequent years suggested a relative risk reduction of 47% (95% CI 32% to 0.59%) for radiographic vertebral fractures and 51% (95% CI 1% to 77%) for hip fractures.

Risedronate is given at a daily dose of 5 mg[43]. Recently two large, 3-year multicenter RCTs have evaluated the efficacy of risedronate in the treatment of postmenopausal osteoporosis[49,50]. In one study, 5 mg of risedronate resulted in a relative risk reduction of 49% (95% CI 27% to 64%) for vertebral fractures[50]. The overall incidence of non-vertebral fractures was reduced by 33% however the results were not significant[50]. In the Harris study[49], treatment with risedronate resulted in a 41% (95% CI 18% to 57%) risk reduction of vertebral fractures and 40% (95% CI 6% to 61%) of non-vertebral fractures. Another study conducted by McClung et al [51] on women 70-79 years of age with osteoporosis with a previous vertebral fracture calculated a relative risk reduction for hip fractures of 60% (95% CI 23% to 77%) and for non-vertebral fractures of 30% (95% CI 10%-50%).

Ibandronate, a daily dose of 2.5 mg, has recently received an indication for the treatment and prevention of osteoporosis in postmenopausal women. In addition to the oral formulation, ibandronate can also be administered intravenously. The effect of ibandronate has been demonstrated in a three-year, randomized, double blind, placebo-controlled, multinational study of 2,946 postmenopausal women aged 55 to 80 years who have had one to four previous vertebral fractures. The incidence of new vertebral fractures was significantly reduced in the ibandronate arm compared to the placebo with a relative risk reduction of 52% (95% CI 29% to 68%), but no significant effect was noted for non-vertebral fractures[52]. The Monthly Oral iBandronate In LadiEs (MOBILE) study, a study conducted in 1,609 women demonstrated that the non-inferiority of once-monthly oral ibandronate to the daily oral regimen. Greater benefit was derived from the ibandronate 150 mg once-monthly tablet than from either the daily regimen or 100 mg once-monthly, without detriment to tolerability[53,54].

Zoledronic acid, the most recent bisphosphonates to be approved for treatment of postmenopausal women is zoledronic acid 5 mg (Aclasta), which is administered as a once-yearly infusion. There is a significant body of clinical experience with zoledronic acid 4 mg (Zometa) for cancer-related bone loss and with Aclasta for the treatment of Paget's disease of bone. Preclinical and clinical studies support the efficacy and safety of this agent in postmenopausal women, and these findings, together with its unique administration schedule, indicate the potential for Aclasta to have a significant impact on the management of postmenopausal osteoporosis. Health Outcomes and Reduced Incidence with Zoledronic acid Once yearly - Pivotal Fracture Trial (HORIZON-PFT)[55], was a 3- year, international randomized, double blind, placebo-controlled phase 3 trial in postmenopausal osteoporosis. Patients in the study were stratified on the basis of whether or not they were receiving concomitant osteoporosis medications (Stratum I: no concurrent medications; Stratum II: concurrent medications taken). A total of 7,765 women were randomized to treatment or placebo. Zoledronic acid treatment resulted in statistically significant improvements in BMD for the total hip, femoral neck, and lumbar spine at all visits (6, 12, 24 and 36 months). The treatment with zoledronic acid resulted in statistically significant reductions in the two primary end points, new morphometric vertebral fractures in Stratum I patients, and new hip fractures in both strata combined throughout the 3-year study. Compared with placebo, zoledronic acid reduced the risk of new vertebral fractures in patients who were not receiving concomitant osteoporosis medications by

70%, and the risk of hip fracture by 41% at 36 months. Zoledronic acid-treated patients also had significantly reduced risks of any clinical fractures (33%), and non-vertebral fractures (25%) compared with placebo group. Moreover, an annual infusion of zoledronic acid within 90 days after repair of a low-trauma hip fracture was associated with a reduction in the rate of new clinical fractures and improved survival[56].

Selective estrogen-receptor modulators (SERMs)

SERMs are non-hormonal agents that bind to estrogen receptors with an affinity equivalent to that of estradiol, but can act either as estrogen agonists or antagonists depending on tissue[40]. Raloxifene is the only SERM approved in some countries for the prevention and treatment of osteoporosis. In early postmenopausal women, raloxifene prevents post-menopausal bone loss at all skeletal sites. The MORE (Multiple Outcomes of Raloxifene Evaluation) study[57], which involved 7,705 women with osteoporosis, noted a 43% (95% CI 3% to 52%) reduction of incident vertebral fractures in women with prevalent vertebral fractures when they were treated with raloxifene. No significant effects on non-vertebral fractures were observed.

Calcitonin

Calcitonin is a naturally occurring peptide hormone. The route of administration is via the nasal mucosa in the form of a spray. The exact mechanism of action is not well understood, however at pharmacological dose levels, calcitonin acts as an anti-resorptive agent. There is only one study[57] to date that has sufficient power and was designed to detect a change in fracture rates. In the PROOF (Prevent Recurrence Of Osteoporotic Fractures) study, a daily dose of 200 IU of nasal salmon calcitonin significantly reduced vertebral fractures by 36% (95% CI 4% to 57%). However the study had a high dropout rate and there was no effect shown for doses of 100 and 400 IU of calcitonin. The study was not powered to detect a reduction in non-vertebral fractures[58].

Parathyroid hormone (PTH)

Clinical studies have been conducted to determine the benefits of parathyroid hormone (PTH) in the prevention and treatment of osteoporosis. A double blind placebo controlled prospective study[59] was conducted in 1,637 postmenopausal women with previous vertebral fractures. Women in the treatment arm received a daily subcutaneous injection of 20 or 40 g. 1-34 fragment recombinant human PTH, for a median of 19 months. The incidence of new vertebral fractures was reduced by 65% (95% CI 45% to 78%) among women treated with PTH.

Strontium ranelate

Strontium ranelate is composed of an organic moiety (ranelic acid) and of two atoms of stable non-radioactive strontium. In vitro, strontium ranelate has been suggested to have a dual effect on bone however, in vivo long term dosing of strontium ranelate in OVX rats and monkeys resulted in increased bone formation but non-significant trends of bone resorption. In human studies (phase III trials), there is some evidence of increases in bone formation markers (serum bone-specific alkaline phosphatase and C-terminal propeptide of type I procollagen) and decreases in markers of bone resorption (serum C-telopeptide and urinary N-telopeptide cross links) from the third month of treatment (2 g of strontium ranelate daily) up to three years[60,61]. Strontium ranelate has been investigated in a large phase III program, included two extensive clinical trials for the treatment of severe osteoporosis. Spinal Osteoporosis Therapeutic Intervention (SOTI) is aimed assessing the effect on the risk of vertebral fractures[62]. TReatment Of Peripheral OSteoporosis (TROPOS) is aimed at evaluating the effect on peripheral (nonspinal) fractures[63]. The study duration was 5 years, with the main statistical analysis planned after 3 years of follow-up. Of 1,649 patients with a mean age of 70 years were included in SOTI and 5,091 patients with a mean of 77 years were included in TROPOS. The primary analysis of the SOTI study, revealed a 41% risk reduction for first new vertebral fracture throughout the 3-year study. The PROTOS study, showed a significant reduction in the relative risk of a first nonvertebral fracture compared with placebo. A 41% reduction in the relative risk of experiencing a hip fracture was demonstrated in the per protocol population.

Alternative or Adjunct Therapies

There are several therapies that are not generally accepted to be the first line treatment for osteoporotic fractures. These medications include hormone replacement therapy (HRT), estrogen derivatives, fluoride, ipriflavone and vitamin K2.

Even though a good-quality body of evidence supports the efficacy of HRT in increasing bone density and decreasing fracture risk,[64] HRT use has declined in recent years due to evidence of increased

risk of cardiovascular complications particularly in aging women[64-66].

Another product often used in many countries is the progestin derivative, tibolone. Tibolone is a synthetic analogue of norethynodrel, a 19 nor-testosterone progestin with weak estrogenic, moderate progestational and mild androgenic properties. Fluoride salts are also available in many countries. Fluoride is one of the few agents that have consistent anabolic effects on cancellous bone mass over a long-term basis, however its effects on reducing vertebral fractures are inconsistent[64].

Ipriflavone, a synthetic phytoestrogen, and vitamin K2 are two other existing treatments where there is some evidence of efficacy. Trials of ipriflavone are difficult to compare because skeletal sites measured in the RCTs vary, and because the RCTs have not consistently ensured adequate intake of calcium and vitamin D in either the treatment or placebo arms[67]. Only one study[68] has reported fracture outcomes. There was no difference in the occurrence of vertebral fractures between the ipriflavone arm and the placebo. Larger studies are required to determine the efficacy of ipriflavone in protecting against vertebral fractures. Vitamin K2 has also been examined to determine its effects on fracture[69-71]. These studies are limited by the fact that the RCTs of vitamin K2 (typically menatetrenone, 45 mg/day) did not include calcium or vitamin D intake in either the treatment or placebo arms[40].

Treatment Guidelines

At present there are no universally accepted guidelines for the treatment and prevention of osteoporosis. Several international and national organizations have published recommendations for treating and managing osteoporosis, including the International Osteoporosis Foundation (IOF)[46], the NOF[61], and the Canadian Medical Association (CMA)[40].

Treatment guidelines endorsed by the IOF recommend that individuals with a fragility vertebral fracture should always be treated, since they are at significant risk of subsequent fractures. Based on the scientific evidence the organization recommends alendronate, risedronate and raloxifene as the preferred treatment options.

The National Osteoporosis Foundation (NOF) has identified cut-points for intervention and recommends initiation of therapy to reduce the risk of fracture in women with[41]:

1) T scores < -2 SD in the absence of risk factors
2) T-scores <-1.5 SD if other risk factors are present
3) All persons 70 years of age and older with multiple risk factors regardless of BMD

The NOF supports the National Academy of Sciences (NAS) recommendation that women over age 50 years consume at least 1,200 mg per day of elemental calcium and an intake of 400 to 600 IU per day of vitamin D[67]. For those at risk of deficiency such as the elderly, the chronically ill or institutionalized individuals, the NOF recommends 800 IU of vitamin D per day[67]. The guideline does not give any specific recommendations of drug therapy but indicates the use of all FDA approved pharmacologic options for the prevention and/or treatment of postmenopausal osteoporosis. The NOF does advocate the use of drugs not approved by the US FDA such as calcitriol, etidronate, newer bisphosphonates (ibandronate, pamidronate, tiludronate, zoledronic acid), sodium fluoride and tibolone[67].

The CMA recommends that bisphosphonates (risedronate or alendronate) should be the first-line therapy for postmenopausal women with low BMD[40]. In addition to these agents or as an alternative, raloxifene should be the first line treatment for postmenopausal women with osteoporosis, especially those women with prevalent vertebral fractures[40]. At present, PTH is not yet approved in Canada, but is expected to become a first-line treatment for postmenopausal women with severe osteoporosis. A second-line treatment recommended for postmenopausal women with osteoporosis is nasal calcitonin[40]. It is recommended that both first-line and second-line treatment should be taken with calcium (1500 mg/day) and vitamin D (800 IU/day)[40].

Economics of Osteoporosis

Burden of Illness - Medical and Societal Needs

Osteoporosis and its direct consequences, fractures, are a major concern for public health, as they represent a significant cost to health care systems in countries such as United States, Canada, the United Kingdom, France, Germany, Italy, and Japan. In the UK, osteoporosis costs the National Health Service (NHS) and the government approximately □1.8 billion each year[72]. According to the IOF audit report "Osteoporosis in European Community: Action Plan" published in 2003, the annual cost of treating all osteoporotic fractures in Europe is estimated to be € 25 billion[73]. Likewise in the United States, it has been estimated that osteoporotic fractures cost US$ 17 billion each year[74].

As the population ages, fracture rates increase exponentially among both men and women. The result is that osteoporosis afflicts an estimated one third of women aged 60 to 70, and two thirds of women aged 80 or older. Accordingly, approximately 200 million women worldwide suffer from osteoporosis. In the UK, the number of women aged 50 years and older who have osteoporosis or are at risk for developing the disease are expected to increase from almost 30 million in 2002 to over 35 million in 2010[72]. Countries within the European Union (EU) are facing a similar trend. The number of prevalent vertebral fractures is expected to rise from 23.7 million in 2000 to 37.3 million by 2050[75].

Osteoporotic fractures are a significant cause of morbidity and mortality. The morbidity burden has considerable medical, social and financial implications that are evident worldwide. Hip fractures have an overall mortality of 15-30%,[21,22] the majority of excess deaths occurring within the first six months after the fracture. These fractures are associated with considerable morbidity necessitating hospital admission for an average of 20-30 days[20]. Moreover, 50% of women who sustain a hip fracture do not return to their previous functional state; approximately 20% require long-term care[23]. Vertebral fractures are also associated with reduced survival[76], but do not have the same degree of impact as hip fracture.

In addition to morbidity and mortality, osteoporotic fractures are associated with significant use of health care resources relating to hospitalization, outpatient care and long-term care. Hip fractures account for more than 20% of orthopaedic bed occupancy in the UK[72]. It is expected that hospital beds needed to treat people with hip and spine fracture will more than double over the next 50 years[19,77]. In Europe and the United States together, of the approximately 650,000 patients per year with hip fractures, more than one-third are rendered functionally dependent (IOF); 19% of the patients enter long-term care facilities[78].

In addition to the direct costs associated with osteoporotic fractures, the indirect costs due to lost of productivity (the value of present production losses resulting from morbidity and future production losses resulting from premature death) and caregiver time should be taken into consideration. In Sweden and the UK the total costs (e.g. primary care, outpatient care and institutional care) of caring for someone with hip fracture is 2.5 times greater than the direct hospital costs[72]. A study of osteoporosis in the United States estimates the value of lost productivity due to missed work at less than 1% of total economic costs whilst the value of premature death accounts for 35.3%[78]. Together the indirect costs of lost productivity and premature mortality from fractures (mostly, but not all related to osteoporosis) amount to between $4.5 and $6.4 billion in the United States alone[78].

Quality of Life Impact of Osteoporosis

Central to the assessment of quality life is the patient's ability to perform the tasks of daily life, engage in social activities, and function without pain. Osteoporotic fractures, particularly vertebral fractures, often cause disability, deformity and chronic pain. More than 50% of hip fracture patients over 60 years of age need more assistance with activities of daily living after fracture than before[79]. Furthermore, Chrischilles et al[23] have estimated that osteoporosis-related fractures will cause 6.7% of women to become dependent in basic activities of daily living during their lifetimes.

The quality of life decreases steadily as the number of vertebral fractures increases. This applies to pain, physical function including activities of daily living (ADL) and mobility, social activities and the perception of being healthy. Patients with two or three vertebral fractures have an increased risk of problems with three or more activities of daily living compared to people without vertebral fractures. Likewise, age also affects the quality of life among patients with osteoporosis as older patients with vertebral fractures can adapt poorly compared to younger patients.

Although there has been increased interest in studies that document the impact of fractures on general health status, as evidenced by development of osteoporosis-specific health status instruments[80,81], very little work has been conducted on utilities for postfracture health states. Utilities represent a person's or a group of people's preference for a health state. Utilities range from 0 to 1, where perfect health is assigned a value of 1 and death is assigned a value of 0. Measurements of utility are different from measurements of general health status (e.g., SF-36) or functional status (e.g., activities of daily living; ADLs), because they reflect how patients feel about what they can do rather than what they are able to do[82]. Commonly used examples of generic instruments for obtaining health state utility values are the EQ-5D and the Health Utility Index-III (HUI-III). Other methods to obtain health state utility values are visual analogue scales, standard gamble and time trade off.

It is evident that with the disability and pain from an osteoporotic fracture, the utility of a fracture state is lower than one's current health state. A study

conducted by Kanis et al in Sweden found the loss of utility in the first year after vertebral fracture was 37% compared with an individual with perfect health[83]. The location of the fracture, time since fracture and presence of a previous fracture can also influence a patient's perception of their health state[83]. The average disutility was greatest in the case of hip fractures over all ages, intermediate for vertebral fractures and lowest for humeral fractures[83]. Zethraeus et al found a 0.32 disutility (reduction in utility) in hospitalized spine fracture patients and a 0.38 disutility in non-hospitalized women who were suffering from a spine fracture[84]. A study conducted by Tosteson et al[85], discovered that mean disutility was 0.18 among women with one or more vertebral fractures and 0.37 among women with hip fracture compared with 0.09 among those without fracture.

Examination of quality of life in the osteoporosis literature has shown that in some situations utility can be negative, which would mean patients perceive a particular health state to be worse than death. A survey of elderly women found that, if given a choice, 80% would choose death over admission to a long-term care facility[86]. Women who had experienced fractures within the past 5 years were willing to give up 6-51% more of their remaining life years to attain perfect health relative to non fracture women[87].

There has also been some research surrounding the impact of fears on quality of life in patients with osteoporosis. The fear of residual disability, and the increased risk of re-fracturing, can seriously jeopardize the quality of life for individuals. Fear, anxiety and depression are frequently reported in women with established osteoporosis[88] and among community dwelling elderly[89].

Recently, new instruments have been developed specifically to measure the health related quality of life (HRQL) impact of osteoporosis (e.g., Osteoporosis Patient Assessment Questionnaire [OPAQ]; QOL Questionnaire of the European Foundation for Osteoporosis [QualEFFO]; Osteoporosis-Targeted QOL Questionnaire [OPTQOL]; Osteoporosis Quality of Life Questionnaire [OQLQ])[90-95]. A number of these disease-specific HRQL instruments have been described in publications in terms of the development and validation processes. Very few have been described in the literature as a measurement tool in patients with osteoporosis, with the exception of the Osteoporosis Quality Life Questionnaire (OQLQ)[94]. Adachi et al[94] studied the effect of vertebral and non-vertebral fractures on HRQL using the mini OQLQ in postmenopausal women 50 years of age and older. Participants were grouped according to incident fracture status: those who experienced clinically recognized incident vertebral fracture and those who sustained incident non-vertebral fractures. Multiple regression analyses revealed that participants who had experienced an incident vertebral fracture had lower HRQL difference scores as compared with non-fracture participants in total scores (-0.86; 95% CI -1.30 to -0.43) including physical functioning, emotional functioning and activities of daily living. Similar results were seen for non-vertebral fracture compared to non-fracture participants in total scores (-0.47; 95% CI -0.70 to -0.25).

Authors' discussion

In Thailand, although osteoporosis is not yet considered to be the national health priority, the disease prevalence and incidence is increasing due to population aging. With the average life expectancy of Thai females of 75 years, women are approaching the risky decade of osteoporotic fractures. When looking into the pragmatic number of the disease occurrence, with almost 6.7 million Thai women over 50 years being diagnosed of osteoporosis using the WHO's criteria, approximately 42,000 hip fractures occurs annually[96]. This can be estimated to the risk of an approximated 2.0% of hip fracture taking place yearly once osteoporosis being diagnosed[96,97] (based on the report by Wainwright, et al. that 46% of fractured patients having osteoporosis and 54% being non-osteoporotic patients[98].

Though there are many guidelines and recommendations issued from countries in the American and European continents, it is inappropriate to adopt these protocols to use as our national guideline without appropriately modification. The authors need to consider the real magnitude of problems on osteoporosis and fractures, its health consequences and taking into account Thai economic and social context. With incomplete information on osteoporosis and its national impact, the authors need to pay more attention to health promotion to prevent osteoporosis and fracture by educating the public to have a healthy lifestyle, avoiding health risk behavior, to maximize peak bone mass and slow bone loss during the climacteric. Fall prevention program including safety landscape, balance training and good visualization should be enthusiastically encouraged. Regulated health measures enacted by governmental health authority may be an effective strategy to assure population health promotion program by linking to health care coverage and

reimbursement. Mass pharmaceutical intervention should be cautiously considered to develop a cost-effective treatment guideline that is relevant to national socio-economic context.

References

1. Johnell O. The socioeconomic burden of fractures: today and in the 21st century. Am J Med 1997; 103(2A): 20S-25S.
2. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis Am J Med 1993; 94: 646-50.
3. Osteoporosis prevention, diagnosis, and therapy NIH Consens Statement 2000; 17: 1-45.
4. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. No. 843 of Technical Reports Series. Geneva: WHO; 1994.
5. World Health Organization. Guidelines for the preclinical evaluation and clinical trials in osteoporosis. Geneva: WHO; 1998: 59.
6. Looker AC, Orwoll ES, Johnston CC Jr, Lindsay RL, Wahner HW, Dunn WL, et al. Prevalence of low femoral bone density in older U.S. adults from NHANES III. J Bone Miner Res 1997; 12: 1761-8.
7. National Osteoporosis Foundation. America's bone health: the state of osteoporosis and low bone mass in our nation. Washington, DC: National Osteoporosis Foundation; 2002: 1-55.
8. Melton LJ III. Epidemiology worldwide. Endocrinol Metab Clin North Am 2003; 32: 1-13.
9. Cooper C, Campion G, Melton LJ III. Hip fractures in the elderly: a world-wide projection. Osteoporos Int 1992; 2: 285-9.
10. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. Osteoporos Int 1997; 7: 407-13.
11. Melton LJ III, Chrischilles EA, Cooper C, Lane AW, Riggs BL. Perspective. How many women have osteoporosis? J Bone Miner Res 1992; 7: 1005-10.
12. A report on Osteoporosis in the European Community. European Commission, 1997. http://europa.eu.int/comm/health/ph_projects/2002/promotion/fp_promotion_2002_a1_04_en.pdf
13. Yan L, Zhou B, Prentice A, Wang X, Golden MH. Epidemiological study of hip fracture in Shenyang, People's Republic of China. Bone 1999; 24: 151-5.
14. Elffors I, Allander E, Kanis JA, Gullberg B, Johnell O, Dequeker J, et al. The variable incidence of hip fracture in southern Europe: the MEDOS Study. Osteoporos Int 1994; 4: 253-63.
15. The Royal College of Physicians. Osteoporosis: clinical guidelines for prevention and treatment. London: Royal College of Physicians; 1999.
16. Kannus P, Parkkari J, Sievanen H, Heinonen A, Vuori I, Jarvinen M. Epidemiology of hip fractures. Bone 1996; 18: 57S-63S.
17. Lau EM, Cooper C. The epidemiology of osteoporosis. The oriental perspective in a world context. Clin Orthop Relat Res 1996; 65-74.
18. Johnell O, Kanis JA, An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 2006; 17(12): 1726-33.
19. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int 2001; 12: 417-27.
20. Johnell O, Gullberg B, Allander E, Kanis JA. The apparent incidence of hip fracture in Europe: a study of national register sources. MEDOS Study Group. Osteoporos Int 1992; 2: 298-302.
21. Keene GS, Parker MJ, Pryor GA. Mortality and morbidity after hip fractures. BMJ 1993; 307: 1248-50.
22. Browner WS, Pressman AR, Nevitt MC, Cummings SR. Mortality following fractures in older women. The study of osteoporotic fractures. Arch Intern Med 1996; 156: 1521-5.
23. Chrischilles EA, Butler CD, Davis CS, Wallace RB. A model of lifetime osteoporosis impact. Arch Intern Med 1991; 151: 2026-32.
24. Kanis JA, McCloskey EV. Epidemiology of vertebral osteoporosis. Bone 1992; 13(Suppl 2): S1-10.
25. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ III. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985-1989. J Bone Miner Res 1992; 7: 221-7.
26. Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, et al. Risk of new vertebral fracture in the year following a fracture. JAMA 2001; 285: 320-3.
27. Lindsay R, Burge RT, Strauss DM. One year outcomes and costs following a vertebral fracture. Osteoporos Int 2005; 16: 78-85.
28. Gold DT. The clinical impact of vertebral fractures: quality of life in women with osteoporosis. Bone 1996; 18(3 Suppl): 185S-9S.
29. Nevitt MC, Thompson DE, Black DM, Rubin SR, Ensrud K, Yates AJ, et al. Effect of alendronate on limited-activity days and bed-disability days

caused by back pain in postmenopausal women with existing vertebral fractures. Fracture Intervention Trial Research Group. Arch Intern Med 2000; 160: 77-85.
30. Cooper C. The crippling consequences of fractures and their impact on quality of life. Am J Med 1997; 103(2A): 12S-7S.
31. Gehlbach SH, Burge RT, Puleo E, Klar J. Hospital care of osteoporosis-related vertebral fractures. Osteoporos Int 2003; 14: 53-60.
32. Burge R, Puleo E, Gehlbach S, Worley D, Klar J. Inpatient hospital and post-acute care for vertebral fractures in women. Value Health 2002; 5: 301-11.
33. Einhorn TA. The bone organ system: form and function. In: Marcus R, Feldman D, Kelsey J, editors. Osteoporosis. San Diego, CA: Academic Press; 1996: 3-22.
34. Lian JB, Stein GS, Canalis E, Gehron Robey P, Boskey AL. Bone formation: osteoblast lineage cells, growth factors, matrix proteins, and the mineralization process. In: Favus MJ, editor. Primer on the metabolic bone disease of mineral metabolism. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 1999: 14-29.
35. MerckMedicus Modules. Osteoarthritis. 2001-2007. Available from: http:// http://merckmedicus.com/pp/us/hcp/diseasemodules/osteoarthritis/diagnosis.jsp
36. The American Medical Association. Managing osteoporosis. Part 1. Detection and clinical issues in testing. Chicago: American Medical Association; 1999.
37. Who are candidates for prevention and treatment for osteoporosis? Osteoporos Int 1997; 7: 1-6.
38. Siris ES, Miller PD, Barrett-Connor E, Faulkner KG, Wehren LE, Abbott TA, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. JAMA 2001; 286: 2815-22.
39. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med 1995; 332: 767-73.
40. Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002; 167(10 Suppl): S1-34.
41. The National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. 2nd ed. Washington, DC: National Osteoporosis Foundation; 2003.
42. Nelson HD, Helfand M, Woolf SH, Allan JD. Screening for postmenopausal osteoporosis: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002; 137: 529-41.
43. Hodgson SF, Watts NB, Bilezikian JP, Clarke BL, Gray TK, Harris DW, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. Endocr Pract 2003; 9: 544-64.
44. Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. BMJ 1994; 308: 1081-2.
45. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med 1992; 327: 1637-42.
46. Delmas PD. Treatment of postmenopausal osteoporosis. Lancet 2002; 359: 2018-26.
47. Cranney A, Guyatt G, Krolicki N, Welch V, Griffith L, Adachi JD, et al. A meta-analysis of etidronate for the treatment of postmenopausal osteoporosis. Osteoporos Int 2001; 12: 140-51.
48. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996; 348: 1535-41.
49. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999; 282: 1344-52.
50. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000; 11: 83-91.
51. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001; 344: 333-40.

52. Chesnut CH III, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004; 19: 1241-9.
53. Miller PD, McClung MR, Macovei L, Stakkestad JA, Luckey M, Bonvoisin B, et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. J Bone Miner Res 2005; 20: 1315-22.
54. Reginster JY, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2-year results from the MOBILE study. Ann Rheum Dis 2006; 65: 654-61.
55. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007; 356: 1809-22.
56. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007; 357: 1799-809.
57. Delmas PD, Ensrud KE, Adachi JD, Harper KD, Sarkar S, Gennari C, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. J Clin Endocrinol Metab 2002; 87: 3609-17.
58. Chesnut CH III, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000; 109: 267-76.
59. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001; 344: 1434-41.
60. Marie PJ, Ammann P, Boivin G, Rey C. Mechanisms of action and therapeutic potential of strontium in bone. Calcif Tissue Int 2001; 69: 121-9.
61. Pors NS. The biological role of strontium. Bone 2004; 35: 583-8.
62. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004; 350: 459-68.
63. Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) Study. J Clin Endocrinol Metab 2005; 90: 2816-22.
64. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D. Guidelines for diagnosis and management of osteoporosis. The European Foundation for Osteoporosis and Bone Disease. Osteoporos Int 1997; 7: 390-406.
65. Waters DD, Alderman EL, Hsia J, Howard BV, Cobb FR, Rogers WJ, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. JAMA 2002; 288: 2432-40.
66. The U.S. Preventive Services Task Force Hormone therapy for the prevention of chronic conditions in postmenopausal women: recommendations from the U.S. Preventive Services Task Force. Ann Intern Med 2005; 142: 855-60.
67. The National Osteoporosis Foundation. Universal recommendations for all patients. Physician's guide to the prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation; 2003.
68. Alexandersen P, Toussaint A, Christiansen C, Devogelaer JP, Roux C, Fechtenbaum J, et al. Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. JAMA 2001; 285: 1482-8.
69. Shiraki M, Shiraki Y, Aoki C, Miura M. Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. J Bone Miner Res 2000; 15: 515-21.
70. Iwamoto J, Takeda T, Ichimura S. Effect of combined administration of vitamin D3 and vitamin K2 on bone mineral density of the lumbar spine in postmenopausal women with osteoporosis. J Orthop Sci 2000; 5: 546-51.
71. Iwamoto J, Takeda T, Ichimura S. Effect of menatetrenone on bone mineral density and incidence of vertebral fractures in postmenopausal women with osteoporosis: a comparison with the effect of etidronate. J Orthop Sci 2001; 6: 487-92.
72. Burge RT, Worley D, Johansen A, Bhattacharyya S, Bose U. The cost of osteoporotic fractures in the UK: projections for 2000-2020. J Med Econ 2001; 4: 51-62.
73. International Osteoporosis Foundation. European union osteoporosis consultation panel.

Osteoporosis in the European community: action plan. Nyon, Switzerland: International Osteoporosis Foundation; 2003.
74. Ray NF, Chan JK, Thamer M, Melton LJ III. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. J Bone Miner Res 1997; 12: 24-35.
75. Finnern HW, Sykes DP. The hospital cost of vertebral fractures in the EU: estimates using national datasets. Osteoporos Int 2003; 14: 429-36.
76. Cooper C. The epidemiology of fragility fractures: is there a role for bone quality? Calcif Tissue Int 1993; 53(Suppl 1): S23-6.
77. Johnell O, Gullberg B, Kanis JA. The hospital burden of vertebral fracture in Europe: a study of national register sources. Osteoporos Int 1997; 7: 138-44.
78. World Health Organization Collaborating Centre. Osteoporosis in the workplace. The social, economic, and human costs of osteoporosis on employees, employers and government. Nyon, Switzerland: International Osteoporosis Foundation; 2002.
79. Sernbo I, Johnell O. Consequences of a hip fracture: a prospective study over 1 year. Osteoporos Int 1993; 3: 148-53.
80. Lydick E, Zimmerman SI, Yawn B, Love B, Kleerekoper M, Ross P, et al. Development and validation of a discriminative quality of life questionnaire for osteoporosis (the OPTQoL). J Bone Miner Res 1997; 12: 456-63.
81. Greendale GA, Silverman SL, Hays RD, Cooper C, Spector T, Kiel D, et al. Health-related quality of life in osteoporosis clinical trials. The Osteoporosis Quality of Life Study Group. Calcif Tissue Int 1993; 53: 75-7.
82. Tsevat J, Weeks JC, Guadagnoli E, Tosteson AN, Mangione CM, Pliskin JS, et al. Using health-related quality-of-life information: clinical encounters, clinical trials, and health policy. J Gen Intern Med 1994; 9: 576-82.
83. Kanis JA, Johnell O, Oden A, Borgstrom F, Zethraeus N, de Laet C, et al. The risk and burden of vertebral fractures in Sweden. Osteoporos Int 2004; 15: 20-6.
84. Zethraeus N, Borgstrom F, Jonsson B. Costs and quality of life related to vertebral fractures: Preliminary results based on an ongoing Swedish prospective study. Abstracts of the IOF World Congress on Osteoporosis. 14-18 May 2004, Rio de Janeiro, Brazil. Osteoporos Int 2004; 15(Suppl 1): S52-S53.
85. Tosteson AN, Gabriel SE, Grove MR, Moncur MM, Kneeland TS, Melton LJ III. Impact of hip and vertebral fractures on quality-adjusted life years. Osteoporos Int 2001; 12: 1042-9.
86. Salkeld G, Cameron ID, Cumming RG, Easter S, Seymour J, Kurrle SE, et al. Quality of life related to fear of falling and hip fracture in older women: a time trade off study. BMJ 2000; 320: 341-6.
87. Tosteson AN, Hammond CS. Quality-of-life assessment in osteoporosis: health-status and preference-based measures. Pharmacoeconomics 2002; 20: 289-303.
88. Gold D. The psychological consequences of osteoporosis, NIH consensus development conference on osteoporosis prevention, diagnosis and therapy. Abstracts of presentations to the conference. March 29, 2000, Bethesda, Maryland.
89. Arfken CL, Lach HW, Birge SJ, Miller JP. The prevalence and correlates of fear of falling in elderly persons living in the community. Am J Public Health 1994; 84: 565-70.
90. Chandler JM, Martin AR, Girman C, Ross PD, Love-McClung B, Lydick E, et al. Reliability of an Osteoporosis-Targeted Quality of Life Survey Instrument for use in the community: OPTQoL. Osteoporos Int 1998; 8: 127-35.
91. Lips P, Cooper C, Agnusdei D, Caulin F, Egger P, Johnell O, et al. Quality of life as outcome in the treatment of osteoporosis: the development of a questionnaire for quality of life by the European Foundation for Osteoporosis. Osteoporos Int 1997; 7: 36-8.
92. Silverman SL, Cranney A. Quality of life measurement in osteoporosis. J Rheumatol 1997; 24: 1218-21.
93. Cook DJ, Guyatt GH, Adachi JD, Epstein RS, Juniper EF, Austin PA, et al. Development and validation of the mini-osteoporosis quality of life questionnaire (OQLQ) in osteoporotic women with back pain due to vertebral fractures. Osteoporosis Quality of Life Study Group. Osteoporos Int 1999; 10: 207-13.
94. Adachi JD, Ioannidis G, Olszynski WP, Brown JP, Hanley DA, Sebaldt RJ, et al. The impact of incident vertebral and non-vertebral fractures on health related quality of life in postmenopausal women. BMC Musculoskelet Disord 2002; 3: 11.
95. Badia X, Prieto L, Roset M, Diez-Perez A, Herdman M. Development of a short osteoporosis quality

of life questionnaire by equating items from two existing instruments. J Clin Epidemiol 2002; 55: 32-40.
96. Lau EM, Lee JK, Suriwongpaisal P, Saw SM, Das DS, Khir A, et al. The incidence of hip fracture in four Asian countries: the Asian Osteoporosis Study (AOS). Osteoporos Int 2001; 12: 239-43.
97. Limpaphayom KK, Taechakraichana N, Jaisamrarn U, Bunyavejchevin S, Chaikittisilpa S, Poshyachinda M, et al. Prevalence of osteopenia and osteoporosis in Thai women. Menopause 2001; 8: 65-9.
98. Wainwright SA, Marshall LM, Ensrud KE, Cauley JA, Black DM, Hillier TA, et al. Hip fracture in women without osteoporosis. J Clin Endocrinol Metab 2005; 90: 2787-93.

โรคกระดูกพรุน: มุมมองในภาพรวมของโรค ระบาดวิทยา การรักษา และเศรษฐศาสตร์สาธารณสุข

ฉัตรเลิศ พงษ์ไชยกุล, ทวี ทรงพัฒนาศิลป์, นิมิต เตชไกรชนะ

โรคกระดูกพรุนเป็นโรคที่มีมวลกระดูกลดลง และโครงสร้างของกระดูกระดับจุลภาคผิดปกติ ส่งผลให้ความแข็งแรงของกระดูกลดลง และเป็นสาเหตุของการเกิดกระดูกหัก เนื่องจากในปัจจุบัน แนวโน้มของจำนวนผู้สูงอายุเพิ่มขึ้นอย่างรวดเร็ว ทำให้โรคกระดูกพรุนกำลังจะเป็นปัญหาทางสาธารณสุขที่สำคัญของประเทศในอนาคตอันใกล้ บทความนี้ได้นำเสนอมุมมองในภาพรวมของโรคกระดูกพรุน ปัจจัยเสี่ยงที่ทำให้เกิดโรคกระดูกพรุนและกระดูกหัก การวินิจฉัยการรักษาโรคกระดูกพรุนในปัจจุบันและข้อมูลทางเศรษฐศาสตร์สาธารณสุข