Osteoporosis: Latest Innovation in Therapy

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Postmenopausal osteoporosis has been found to be a health threat in most developed countries and is an emerging problem of countries in Asia Pacific region. It is estimated that half of all hip fractures worldwide will occur in this region by 2050. The consequences of osteoporosis are fractures which may have a highly impact on quality of daily life. The current conceptual understanding of osteoporosis is emphasized on bone strength. It is defined as an integration of bone density and bone quality. Assessment of treatment efficacy is more accurate by looking at fracture risk reduction over an increase of bone mineral density. The premature termination of the Women's Health Initiative study in July 2002 has limited the osteoprotective role of hormone replacement therapy (HRT). It is a general recommendation to give HRT to symptomatic women in their perimenopause or climacteric midlife. Non-HRT anti-osteoporotic medication eg., raloxifene, bisphosphonates, calcitonin, and intermittent PTH is considered to be the first line therapy in asymptomatic women over 60 years. Other innovative anti-osteoporotic regimens are being under research development.

Keywords : *Osteoporosis, Innovation, Therapy*

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Osteoporosis: health burden and epidemiology

During the last decade, osteoporosis has received more scientific and public attention. It has been considered to be a major health threat in the United States and several European countries and seems to become an increasing health problem in various countries in Asia Pacific region.

It is generally perceived that the serious consequences of osteoporosis are fractures, most frequently occur in the vertebrae, hip and wrist. Spinal fractures can result in significant morbidity whereas hip fractures result in substantial high morbidity and mortality. Several health sequele associated with osteoporosis have high impact on quality of daily life involving functional limitations, acute and chronic pain, social role loss and isolation, and psychological dysfunction which can be serious and debilitating[1].

Osteoporosis is most prevalent amongst postmenopausal women[2,3]. The lifetime risk of osteoporotic fracture for a woman at the menopause in many Occidental countries is 30-40%[4]. In 1998, the Asian Osteoporosis Study Group[5] conducted a survey on the incidence of hip fracture in women and men residing in countries around the Asia Pacific region. They found that women in Asia had a lower incidence of hip fracture compared to their Caucasian counterparts[6,7] (Fig. 1). On the other hand, it is difficult to compare the prevalence of vertebral fracture in different countries for these can easily be affected by

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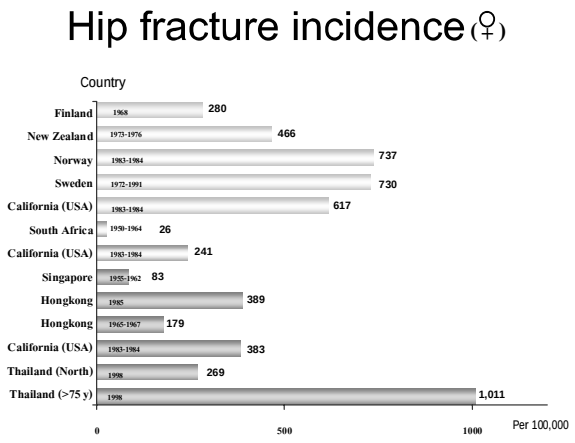

Fig. 1 Age-adjusted rate of hip fracture per 100,000 female population by country and year of study

differences in radiographic methods and fracture definition[2].

As a matter of fact, there have been great geographic variations in the prevalence of osteoporosis. For instances, using World Health Organization criteria, 13-18 per cent of women in the United States older than 50 years have osteoporosis[8], 22 per cent of women in England and Wales older than 50 years have femoral neck osteoporosis[9], 24 per cent of Japanese women aged 50 years or older are afflicted with osteoporosis[10]. In Tailand, the prevalence of spines (L1-L4) and femoral neck osteoporosis in women aged over 40 years was reported between 19-21 per cent and 11-13 per cent respectively[11,12].

Osteoporosis has reached epidemic proportions in most of the developed countries, but the problem is just emerging in Asia. It has been estimated that 1.7 million hip fractures occur annually around the world, with one third in Asia. Nevertheless, half of all hip fractures in the world will occur in this region by the year 2050 and this will amount to 3 million per year[13].

The association of osteoporosis and estrogen deficiency after menopause has been reported since 1941 based on the original work of Albright and colleagues[14]. Since then there was a large volume of evidence that supported the critical role of estrogen as an antiresorptive agent. Nonetheless, after the first report of the Women's Health Initiative on July 2002[15], the osteoprotective role of hormone replacement therapy (HRT) has been put into dilemmas. Clinicians are more cautious to use HRT in asymptomatic postmenopausal women aged over 60 years[16]. Choices of innovative treatment are highly demanded to ensure safe prescription for women who no longer benefit from HRT.

Osteoporosis: bone mineral density versus bone strength

In 1991, the Consensus Development Conference has defined osteoporosis as a progressive, systemic skeletal disease characterized by low bone mass and deterioration of bone microarchitecture, leading to increased bone fragility and susceptibility to fractures[17]. For the diagnostic purposes, the World Health Organization has defined osteoporosis as a bone mineral density (BMD) value at least 2.5 standard deviations (SD) below the young adult mean (T-score < -2.5)[18,19].

In 2000, the National Institutes of Health (NIH) organized a Consensus Development Conference and re-defined osteoporosis as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. The Panel defined bone strength as the integration of bone density and bone quality. Of which the latter refers to architecture, turnover, damage accumulation (eg., microfractures), and mineralization[20].

Currently, there is no accurate measurement of bone strength particularly bone quality. Bone mineral density is frequently used as a proxy measure and accounts for approximately 70% of bone strength[20]. As a matter of fact, there is an interplay of pathogenetic factors leading to osteoporotic fractures (Fig. 2)[21,22]. It is, therefore, more appropriate to assess treatment efficacy looking at the final endpoint ie., fracture frequency which imply bone strength and bone quality rather than focussing on intermediate outcome ie., bone mineral density.

Osteoporosis: HRT conundrum

The classic studies by Claus Christiansen[23] and Robert Lindsay[24] in the early 1980s have frequently been quoted to support the use of HRT for osteoprotective purpose. Estrogen was believed to have beneficial effects on cardiovascular and neurological systems. With a huge volume of optimistic observational studies, some clinicians prescribed HRT to all women after menopause.

The first conceptual turning point probably took place in 1998 after the report from "Heart and Estrogen/Progestin Replacement Study (HERS)"[25]. The results revealed no beneficial effect of estrogen on secondary prevention of coronary heart disease.

In 2001, Manson and colleague[26] conducted an excellent review on benefits and risks of HRT based on hierarchy of evidence. The authors concluded that

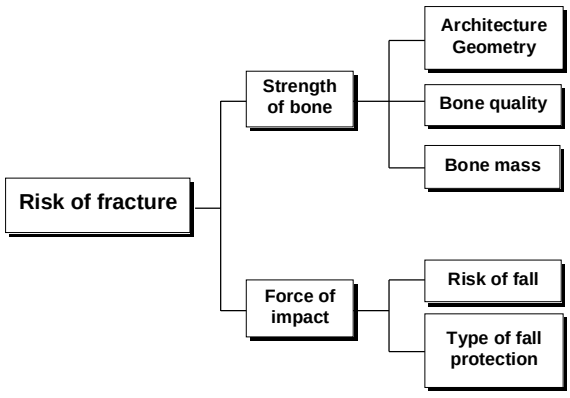

Fig. 2 Schema to demonstrate the determinants of fracture risk

the definite benefits of HRT were the relief of menopausal symptoms and risk reduction of osteoporosis. The definite risks included increased risks of venous thromboembolism and endometrial cancer in those who were long-term users of unopposed estrogen. Other "probable" benefits and risks of HRT include primary prevention of coronary heart disease, risk reduction of dementia, non-vertebral fractures, colorectal cancer and the increased risk of breast cancer and strokes.

In 1992, a large prospective study, namely, Women's Health Initiative (WHI), was conducted in 40 studied sites in the United States, primarily looking at the effects of HRT on fractures, cancers and cardiovascular diseases[27]. The first report of WHI appeared on July 2002[15] which can be simply concluded as the followings : firstly, the risks of combination estrogen and progestin exceeded benefits in healthy postmenopausal US women. Secondly, the risks of HRT on cardiovascular diseases, dementia and breast cancer appeared to be higher among aging postmenopausal women.

In April 2004, the remaining hormone study arm of the WHI ie., estrogen replacement study (ERT), has been released after approximately 7 years of follow up[28]. The results revealed that there was a significant increase in the risk of stroke and deep vein thrombosis in the treatment group when compared to the placebo. The study confirmed risk reduction of hip and vertebral fractures but did not show significant difference among the groups on coronary heart disease, pulmonary embolism, breast and colo-rectal cancers, overall mortality and global index.

These studies imply that the previous thought of one-size-fit-all is no longer appropriate. Use of HRT has been evolved from standardized regimen to individualized adapted dose. It is a safe practice to carefully look into individual indication, contraindication, special precaution and give HRT for symptomatic women during their perimenopause or climacteric midlife.

Women in this age are more common to suffer from menopausal symptoms due to erratic changes of circulating estrogen. The use of HRT to prevent bone loss in symptomatic women is considered to be an acceptable approach. Woman with premature ovarian failure or induced menopause prior to the usual menopausal age eg., surgical menopause, radiation/ chemotherapeutic induced menopause, are good candidates for hormone replacement.

At present, there appear to be a general trend to prescribe HRT/ERT to younger menopausal women and give non-HRT antiresorptives such as bisphosphonates, raloxifene, intermittent parathyroid hormone (PTH) to women at higher age. Non-medical modalities such as lifestyle modification should be taken into account as an initial osteoprotective strategy.

Osteoporosis: Present and future of new therapeutic options

In the absence of estrogen deficiency symptoms, HRT is not recommended for fracture prevention particularly in women over 60 years[16,29]. General approach for osteoporosis treatment are as the followings[16]: raloxifene and bisphosphonates may be appropriate in the later postmenopausal years, use bisphosphonates in women aged over 75 years when the main concern is preventing hip fracture, intermittent parathyroid hormone should be considered in patients with severe osteoporosis and fractures, give calcium supplements in people aged over 65 years, and vitamin D if deficiency is present or likely.

Alternatively, postmenopausal women can be treated with tibolone, a synthetic sex hormone derivative that does not possess side effects of estrogens on breast, cardiovascular system and prevents postmenopausal bone loss[30]. Although the results from the Million Women Study[31] investigated the effect of various patterns of hormone therapy use on incidence of fracture showed that current users of tibolone significantly decreased the risk of incident fracture compared to never users, there are no prospective, randomized trial data available that support the use of tibolone in preventing osteoporosis-related fractures.

Raloxifene (60 mg/day) has been found to reduce the risk of new vertebral fractures in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial[32]. In addition, a post hoc analyses study found that raloxifene decreased non-vertebral fracture risk in the subgroup of women with severe vertebral fractures at baseline[33]. Indeed, they appear to reduce the risk of estrogen-receptor-positive breast cancer, an important secondary benefit in older women.

Two bisphosphonates, alendronate and risedronate, are available as daily dose of 10 and 5 mg and as a once-weekly dosage of 70 and 35 mg, respectively[34]. Directly treating bone resorption, bisphosphonates are a group of medication ideally suited to treatment of osteoporosis and fracture risk reduction [35]. Alendronate may cause unwanted gastrointestinal side effects but the problem is avoided if it is given once weekly[36]. Risedronate was found in one study[37]

to have lower incidence of gastrointestinal erosion than alendronate but not in another[38].

Calcitonin, an endogenous peptide that inhibits osteoclastic activity, is available in nasal and subcutaneous forms that make it an appealing alternative for women who do not tolerate raloxifene or bisphosphonates. It should be relegated to second-line therapy, however, because of the lack of convincing fracture efficacy[39].

Teriparatide, a recombinant parathyroid hormone 1-34, given as intermittent injections have an anabolic effect on the skeleton, restoring bone strength by stimulating osteoblastic rather than osteoclastic activity[19,40]. Intermittent PTH is the only available bone formative agent in contrast to most of the antiresorptive medication currently appears in the market.

Other in-pipeline therapeutic strategy includes Zoledronate, another potent nitrogen-containing bisphosphonate, is being in phase III development for administration by once yearly infusion[41], strontium ranelate promotes bone formation by stimulating osteoblasts and reduces bone resorption by inhibiting osteoclast activity and differentiation[42]. Results from two large phase III studies indicate that strontium ranelate is likely to be a promising future option in the prevention of postmenopausal osteoporosis[19].

Acknowledging the limitations of these medications which act through different mechanisms, there has been increasing interest in using these therapies in combination as a way of increasing their benefits. Although the results of some short-term studies showed greater bone mineral density with more therapies, they lacked the statistical power to demonstrate any additional contribution to fracture reduction[43].

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โรคกระดูกพรุน: นวภาพล่าสุดในการรักษา

นิมิต เตชไกรชนะ, ไพโรจน์ วิทูรพณิชย์

โรคกระดูกพรุนเป็นปัญหาทางสุขภาพที่พบได้ส่วนใหญ่ในประเทศที่พัฒนาแล้ว และกำลังพบเป็นปัญหาสำคัญในประเทศในภาคพื้นเอเชียแปซิฟิก มีประมาณการณ์ไว้ว่า ในปีพ.ศ.2593 ครึ่งหนึ่งของผู้ที่มีกระดูกสะโพกหักจะอยู่ในภาคพื้นดังกล่าว ผู้ที่มีโรคกระดูกพรุน จะมีกระดูกหักได้ง่าย ซึ่งมีผลต่อคุณภาพชีวิตและการดำเนินชีวิตประจำวันอย่างมาก ความเข้าใจในเชิงแนวคิดเกี่ยวกับโรคกระดูกพรุนในปัจจุบันเน้นที่ความแข็งแกร่งของกระดูก ซึ่งประกอบด้วยปัจจัยในเรื่องความหนาแน่นของกระดูก และคุณภาพของเนื้อกระดูก ดังนั้นการประเมินผลของการรักษาใด ๆ ควรพิจารณาผลต่อการลดความเสี่ยงต่อกระดูกหักมากกว่าการดูผลในการเพิ่มความหนาแน่นของกระดูก ผลการศึกษาจาก Women's Health Initiative ในปี พ.ศ. 2545 ซึ่งยุติก่อนกำหนด จำกัดบทบาทของการใช้ฮอร์โมนทดแทนในการรักษาโรคกระดูกพรุนลง จึงเป็นข้อแนะนำกันโดยทั่วไปว่า ควรให้ฮอร์โมนทดแทนในสตรีวัยหมดระดูที่มีอาการของการหมดระดู ที่ยังอยู่ในวัยใกล้หมดระดู หรือ ระยะกลางของวัยเปลี่ยน การเลือกใช้ยารักษาโรคกระดูกพรุนในกลุ่มที่มิใช่ฮอร์โมนทดแทน ได้แก่ raloxifene, bisphosphonates, calcitonin และ PTH ควรใช้เป็นยาอันดับแรกในสตรีที่มีอายุเกิน 60 ปี ที่ไม่มีอาการของการหมดระดู ปัจจุบันยังมียาที่ใช้รักษาโรคกระดูกพรุนที่ยังคงอยู่ในระหว่างการวิจัย