Treatment and Prevention of Osteoporosis in Menopause

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Dating back to 1991, osteoporosis was defined by its pathologic physiology. The three important keywords in the definition include low bone mass, microarchitectural deterioration and susceptible to fracture. The disease has become measurable since the introduction of WHO's criteria in 1994 of bone mineral density (BMD) more than 2.5 standard deviations below the young adult average value. Nonetheless, the criteria is probably misled the therapeutic threshold which overemphasizes the important of BMD on treatment decision. The recent definition of osteoporosis by US-National Institute of Health (US-NIH 2000) has taken bone quality into consideration. The term "bone quality" includes bone architecture, geometry, bone turnover, degree of mineralization, accumulated damage and property of collagen and mineral matrix. Use of BMD only for treatment decision is no longer appropriate due to the fact that most of fracture events occur in osteopenic patients.

Clinical risk assessment of osteoporosis and fractures is an initial step prior to treatment consideration. Further assessment of bone density using Dual Energy X-ray Absorptiometry (DXA) is not cost benefit, if it is performed as a routine in women after menopause. Recently, the Osteoporosis Self-assessment Tool for Asian (OSTA) has been developed by an Asian Research Group to help identify those who are high risk for osteoporosis. The OSTA's formula is 0.2x (body weight in kilogram-age in years). If the score is below -4 this is considered to be high risk. The value above -1 is low risk and should not proceed to DXA unless having other risk factors. There are attempts to combine various risk factors such as BMD, bone markers, history of previous fractures to estimate future fracture proba-bility. This is supposed to be a more accurate tool for risk evaluation and therapeutic intervention to reduce any inappropriate treatment when used BMD alone as the intervention threshold.

In general, bone loss is more apparent in women than men after menopause. After peak bone mass, bone loss is gradually taking place due to a negative bone balance resulting from the decrease in bone formation. After cessation of menstruation, when circulating estrogen decreases, bone resorption activity increases to a significant level. The developmental cascade of osteoclasts (bone resorbing cells) which are derived from hematopoietic stem cells, need certain cytokines from the osteoblasts (bone forming cells). With estrogen deficiency, monocytes increase the production of certain cytokines, i.e., interleukin-1 (IL-1) and tumor necrosis factor (TNF) which stimulate stromal cells and pre-osteoblasts to release a number of factors including IL-6, macrophage colony stimulating factor (M-CSF), IL-11, granulocyte-macrophage colony stimulating factor (GM-CSF), transforming growth factor beta (TGF-b) and the recent discovered pivotal factor ie., the receptor activator of nuclear factor kappa B ligand (RANKL). These cytokines accelerate the progression of osteoclast cascade resulting in increasing bone resorption.

In estrogen replenished state, RANKL is binding to osteoprotegerin (OPG) which is a soluble decoy receptor for RANKL. The decline in the level of estrogen lowers the level of OPG resulting in more RANKL being available to bind to RANK on the osteoclast progenitor, therefore stimulation of osteoclast formation and activity. Estrogen therapy exerts its antiresorptive effects by inhibition of osteoclast recruitment, osteoclast activity and shortening its lifespan (inducing apoptosis), as a consequence, retarding resorption cycle and having more time for bone matrix formation and mineralization.

Before 1998, estrogen has been prescribed for the treatment of menopausal symptoms, prevention of osteoporosis and coronary heart disease. After the results from the Heart and Estrogen/Progestin Replacement Study (HERS) in 1998 and a series of reports from the Women's Health Initiative during 2002-2004, US-Food and Drug Administration (US-FDA) and various menopause societies worldwide have issued guidelines / position statements to use hormone therapy (HT) with more precaution. It is generally accepted to use HT in those who have moderate to severe menopausal symptoms including those who have osteoporosis if benefit outweighs risk. The use of HT appears to be more acceptable in younger women such as those with premature ovarian failure (premature menopause, age < 40 years), women in their early menopause (<45 years) or perimenopause.

The results from these randomized trials have revealed possible risks of long-term HRT in healthy postmenopausal women particularly those over 60 years. Accordingly, it is preferable to prescribe non-HT medication for the treatment of osteoporosis in women after 60 years. The pharmaceutical agents that have undergone extensive clinical trials include the antiresorptive category for instance, bisphosphonates, raloxifene, calcitonin, calcium and vitamin D. For bone forming category includes intermittent PTH and strontium ranelate.

In current clinical practice, bisphosphonates seem to be the drug of choice for fracture prevention. Most of the trials revealed its efficacy on the reduction of vertebral and non-vertebral fractures. Though there is concern over its gastrointestinal side effects with daily dose, the problem is much less significant when the once weekly

regimens are available. However, there is a nine-case report of severe suppression of bone turnover with long-term bisphosphonate therapy. The findings raise the possibility of increased susceptibility to fracture and delayed fracture healing. Some animal studies with high doses of bisphosphonates revealed microcrack accumulation. Concern of bone overmineralization and an increase in bone fragility in long-term use need a close follow up. Until now, the longest duration of placebo-controlled trials is six years and subjects in observational studies have used the newer amino-bisphosphonates for ten years. So far, there has been no conclusive human report on the long-term adverse events. There is still controversy over the benefit of fracture reduction if the drug is continued after five years.

Raloxifene is another osteoprotective option that has been proved of its efficacy on the reduction of vertebral fractures. The efficacy on non-vertebral fractures has been shown later in the secondary analysis of those with severe vertebral fractures. Its non-osteoporosis benefit is the decrease in the risk of estrogen-receptor-positive breast cancer. Its cardiovascular benefits are needed to be confirmed. On the contrary, raloxifene may exacerbate vasomotor symptoms (VMS) particularly in perimenopausal women. The Multiple Outcome of Raloxafene Evaluation (MORE) trial revealed an increased risk of venous thromboembolism (VTE) as high as those found in women taking HT. However, the multi-center study in the Asia-Pacific region did not reveal higher incidence of VMS and VTE in the treatment over placebo.

Calcitonin is sometimes used, but parenteral administration can have unpleasant side effects and its nasal form is relatively weak in its effect on BMD and fracture incidence. Calcium can decrease bone turnover and bone loss in certain condition. When given with vitamin D, it was found to diminish hip fractures in the elderly institutionalized patients. However, calcium is commonly given in adjunct to patients receiving an antiresorptive treatment. Vitamin D should be given in sufficient amounts in case that sunlight exposure is inadequate. The addition of 400-800 U is generally recommended for elderly Caucasians.

The main aim of future therapy is to try to increase bone formation. It was shown recently that daily administered dose of parathyroid hormone increases bone formation, bone mass and reduces the fracture incidence. However, it should be given in very advanced cases of osteoporosis. It has not yet been advocated for less disabling cases or for prevention.

As in a familiar proverb: "Prevention is better than cure," the cost of prevention is much less than that of treatment and rehabilitation. We need to put more attention on national health promotion and disease prevention as in the case of osteoporosis. Firstly, try to increase peak bone mass in young individuals to the maximum of one's genetic allowance. This can be done by encouraging healthy lifestyles and avoiding unhealthy behaviors. Secondly, try to reduce bone loss after menopause. Lifestyle modification with or without adjunction of appropriate medication to optimize bone turnover may help reverse the rapid loss, as a consequence, reducing risk of fractures. Lastly, try to reduce the risk of fall or minimize traumatic impact. These can be done by keep an appropriate exercise program to strengthen bone, muscle and overall health. Mental exercise is another issue that is less documented and researched on. The mind-and-body co-ordination with full mental awareness in every motion is a good strategy to keep balance and fall prevention. As a matter of fact, fractures depend on bone strength and fall. Without fall, fracture probability decreases even with low bone mass.

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