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Current Options and Future Directions for Managing Osteoporosis: An update

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Introduction

Osteoporosis is considered as the most common metabolic bone disorder and characterized by low bone mass and skeletal fragility. Osteoporosis engages approximately about 200 millions of individuals, world widely. For instance, about 10 millions of Americans are affected and another 34 million are at risk of osteopenia [1]. Osteoporosis has been known as a silent disease. The affected patients do not often understand about the nature of their disease until it significantly develops so that the patients are often presented with osteoporosis related fractures [2]. Postmenopausal women are the most commonly affected population in the world and the fracture rates in postmenopausal Asian, American and African women have been reported to be 41, 54 and 91%, respectively [3]. During the post-menopausal period, the risk of fractures increases due to the accelerated bone loss because estrogen declines with age. Moreover, men are also affected by osteoporosis with the incidence of 20% [4]. Annually, $19 billion are accounted for osteoporotic fractures in health care expenditures which expected to rise to $25.3 billion in the future 10 years [5]. Each year, nearly 300,000 hip fractures, 547,000 vertebral fractures and almost 1,054,000 other fractures occur due to osteoporosis. Osteoporosis imposes more than 432,000 hospital admissions, 2.5 million medical office visits, and 180,000 nursing home admissions to the healthcare systems, annually [6]. Despite of several attempts, osteoporosis is still a considerable challenge for the governments.

Osteoporosis occurs when the balance between bone formation and bone resorption alters. Bone remodeling process consists of two main parts including bone formation by osteoblasts and bone resorption by osteoclasts. These parts are under a haemostatic control in viable bodies. In such imbalances of osteoblastic and osteoclastic activity, resorption exceeds the formation, bone density decreases and osteoporosis occurs in patients [7]. There are numerous risk factors that predict osteoporosis/osteopenia that may lead to osteoporotic fractures. These risk factors include age, Caucasian, smoking, female gender, medications, physical inactivity, and others. Each risk factor has a different influence on the development of osteoporosis [8]. Osteoporosis is often a silent disease because at the onset there are no obvious indications. However, there are some symptoms that may appear over time including loss of height (patients may lose 10-15 cm in height due to the compression fractures in the spine and collapsing vertebrae), back or neck pain (almost, this is very painful because the collapsed vertebrae may pinch the nerves that radiate out from the spinal cord and typically in the lower thoracic and lumbar areas, T5-L5), stooped posture (the compression of the vertebrae may also cause kyphosis or curvature of the upper back), and fracture (occurring with fall or even a minor movement) [9].

There is a big challenge for orthopedic surgeons and other clinicians to diagnose, prevent, and treat osteoporosis before fractures occur. According to the American Association of Clinical Endocrinologists (AACE) and National Osteoporosis Foundation (NOF) guidelines, postmenopausal women and 50 year old men or older who have the following criteria should be considered for treatment: Hip or vertebral (clinical or morphometric) fracture, spine or femoral neck T-Scores of <-2.5 (after evaluation has excluded secondary causes), Low bone mass (T-score < -1.0 but > -2.5) and 10-year probability of hip fracture >3% or 10 year probability of major osteoporosis-related fracture >20% [10]. For treatment of osteoporosis, numerous options exist including diet/supplementation, exercise, medications and combination therapy [10].

Exercise and physical fitness is a useful way in public health promotion for many reasons, including reduction in the risk of heart disease, reduction blood pressure, and contribution to control diabetes, reduction in cholesterol levels and improving mental health as well as promoting musculoskeletal system [11]. For osteoporotic patients, exercise may specifically increase BMD and total body calcium level. Many studies have documented which have shown that people who exercise regularly have higher bone density than the inactive individuals [12]. The beneficial physiologic effect of exercise, most likely, results due to repeated loading and stress upon musculoskeletal system. The mechanical strain on bone structure may induce osteoblast to produce new bone as well as inhibit osteoclast to resorb the osteoid [12]. Particularly, aerobic exercises such as running, biking, skating and wrestling have more beneficial effects on bone health. The NOF has recommended a combination of aerobic and anaerobic exercises for prevention of osteoporosis [10]. The training programs which were prescribed by clinicians will depend on the interests and more importantly the ability of the individual patient.

Unfortunately, some of the osteoporosis conditions are complicated with other diseases such as osteoarthritis; therefore regular exercise for such patients would be very difficult to be done. However, the patients should be encouraged to exercise for at least 30 minutes a day and if they tolerate such program then it should be developed to at least 5 days per week [10-12]. Using proper diet and supplementation with calcium, vitamin D and phytoestrogens are also very necessary for prevention and treatment of osteoporosis. To prevent excessive bone mineral loss, an adequate amount of calcium must be administered. According to the NOF recommendations, the 50-year old and older patients require elemental calcium (1200 mg/day) and should obtain 800-1000 IU of vitamin D per day. In the older individuals, the problem of calcium absorption from the gastrointestinal tract is more acute. Increasing overall calcium intake and maintaining adequate levels of vitamin D may overcome this problem [13]. The three main dietary types of phytoestrogens including isoflavones, coumestans, and

lignans may be found in particular foods such as beans, cabbage, rice, berries, sesame seeds, and grains. The results of clinical trials about the efficacy of phytoestrogens on osteoporosis, remains conflicting. For example, in the East Asian countries (where higher dietary intake of phytoestrogens occurs) lower rates of hip fracture but relatively similar rates of spine fractures have been cited when compared to other regions [14,15].

Osteoporosis may be treated with several medications which can be divided into three main categories including anabolic, catabolic and dual-mode action agents. Antiresorptive therapies include estrogen, selective estrogen receptor modulators (SERMs), bisphosphonates, and calcitonin that their major merit is to reduce bone loss [16-18]. Teriparatide is the only FDA approved anabolic agent which is a synthetic form of parathyroid hormone. Teriparatide specifically increases the number of osteoblasts through preventing the osteoblast apoptosis and inducing the osteoprogenitor cell differentiation into osteoblasts in the bone marrow. This therapeutic modality has been recommended as the last resort in patients who have failed other treatment regimens [19].

The effectiveness of these therapies and their combinations on various osteoporosis conditions are under investigation and development. Hormone therapy (e.g. estrogen, progesterone and their combination) in postmenopausal women is an old option in preventing and treating osteoporosis. Estrogen increases bone formation by inducing osteoblastic activity leading to greater pro-collagen and alkaline phosphatase production. In addition, it inhibits bone resorption by suppressing osteoclastogenesis. The use of post-menopausal hormone therapy (HTP) has been declined in the early 2000s because of their potential in carcinogenesis. This carcinogenic effect is directly proportional to the administrated dose and dosage. Because, the benefits of HTP are time dependent and the discontinuation of the treatment often relapse the deterioration; long time HTP may lead to increase the chance of carcinogenesis and serious side effects particularly the breast tumor as well as stroke, venous thromboembolism, and coronary disease in postmenopausal women. The scientists have concluded that estrogen therapy is not recommended unless the benefits of fracture reduction would be greater than the risk of cardiovascular diseases and breast cancers [20,21].

SERMs are a class of compounds that interact with intracellular estrogen receptors and mimic the effects of estrogen on the bone, heart, uterus and central nervous system, and antagonize the estrogen effects on the breast. For example; tamoxifen acts as estrogen in the bone and uterus (agonist) while it acts as an antagonist of the estrogen in the breast, thus long term administration of tamoxifen although reduces the chance of breast cancer, but it significantly increases the chance of uterine cancer due to the agonistic effects of estrogen on uterus. Thus tomoxifen should only be given in patients that have breast cancer but their uterus has been removed surgically. Raloxifene is the second generation of the SERMs that is FDA has been approved and its estrogenic effects on the uterine tissue is reduced. Thus it is safer than the tomoxifen and can be administrated to those patients that still have their uterus. Raloxifene has been shown to increase bone mass, structurally recover bone, and decrease the risk of vertebral fractures [22,23]. Raloxifene is contraindicated in lactating women who are or may become pregnant (because of teratogenic effect) and in patients with a history of clotting disorders, such as venous thromboembolism. Bazedoxifene (a third generation SERM) has been approved for the treatment of osteoporosis by the European Medicines Agency since 2009. In a randomized controlled trial study, the bazedoxifene efficacy has been compared with raloxifene and placebo in osteoporotic postmenopausal women. It showed that the incidence of new vertebral fractures was significantly lower in all the treated subjects compared with the placebo group. Bazedoxifene also improved BMD and reduced the level of bone markers. It is in the late phases of review by the FDA [24].

Another antiresorptive drug that has been used in the treatment of osteoporosis is the bisphosphonates. Bisphosphonates decrease bone resorption by induction of osteoclast apoptosis and reducing the function of osteoclasts. Several medications or drug combinations have been approved by FDA for the prevention and treatment of osteoporosis, including alendronate with or without vitamin D, ibandronate, risedronate with or without calcium supplement, and zoledronic acid. Bisphosphonates are the best candidate for treating severe osteoporotic patients, with beneficial effects typically seen within a year [25]. A second-generation bisphosphonate, alendronate, has been shown to be one of the most effective therapeutic agents for patients with T-scores less than -2.5 or for those that have previous vertebral fractures. Oral dose of alendronate is 5 mg/day for prevention and 10 mg/day for treatment of osteoporosis. It can also be administrated as 35-mg and 70-mg once a week [26]. Zoledronic acid, a third generation and a very potent drug of bisphosphonates, may be given as 5 mg infusion once per year for treatment of osteoporotic patients who are at high risk of fracture. The most common side effects of bisphosphonates are on gastrointestinal tract, including initiating esophagitis and gastric ulcer [25,26].

In 2011, FDA approved a new drug called denosumab for treatment of osteoporosis in patients at increased risk of fracture. It is a fully human monoclonal antibody that has been designed for the treatment of osteoporosis, rheumatoid arthritis, and multiple myeloma. Denosumab mimics osteoprotegerin (an endogenous RANKL inhibitor) by binding to and inhibiting the receptor activator of the nuclear factor kappaB ligand (RANKL). RANKL controls the maturation and survival of osteoclasts. Clinical trials have shown a significant reduction in hip, vertebral and nonvertebral fractures without having any adverse effects (e.g., cancer, delayed healing, osteonecrosis of the jaw, injection site reactions) in the denosumab treated group [27,28]. Calcitonin-salmon (Miacalcin®) is approved by FDA for the treatment and prevention of osteoporosis in women that are in their postmenopausal period for at least 5 years. It has not been recommended as a first-line treatment and its application has been suggested when the alternative treatments would not be a suitable options. In the proper dose, it is an inhibitor of bone resorption. Oral and inhaled forms of calcitonin are under development. The data and evidences regarding the use of calcitonin in reducing hip fractures or preventing any fractures in osteoporotic patients are conflicting. However calcitonin at least may help in patients with acute vertebral fractures due to a possible analgesic effect and in combination therapy, it may decreases the risk of gastrointestinal upset (i.e., bisphosphonates) and thromboembolism (i.e., SERMs) associated with other bone anabolic agents [29].

Many clinical and experimental studies have suggested that statins are beneficial for treatment of osteoporosis. The lipophilic statins such as simvastatin may be the most effective agent in increasing BMD among all the statins. Most investigators suggested that these beneficial effects are dose-related and achieved by much higher doses than the clinical doses through the same route of administration [30-31]. A relatively new drug, strontium ranelate, is currently approved in

Europe for the prevention and treatment of osteoporosis in postmenopausal women. Strontium ranelate is a dual-action mode agent that is capable of both promoting bone formation and inhibiting bone resorption. Long-term therapy in osteoporotic patients with strontium ranelate has proven its effectiveness in reducing fracture risk. However application of strontium ranelate is strictly inhibited to those that have severe osteoporosis degree [32].

Combination therapy for osteoporosis has been evaluated in many clinical trials with various combinations in order to find out the best option and formulation. These therapies have been categorized into two main groups including combination of anabolic agent with antiresorptive agents and combination of two antiresorptive agents [33]. Initially, researchers hoped that combination of bisphosphonates and PTH that are given simultaneously would lead to more beneficial effect compared to mono-therapy. However, evidences showed that negative effects with the two agents when they are given together, although a combined consecutive therapy with bisphosphonates and PTH were more promising [34]. Combination therapy of SERMs and PTH is another option that the efficacy of this latter option has been proved both in vivo and in the clinical setting. The results from such studies illustrated that the anabolic effects of PTH could be enhanced through combination with raloxifene [35]. Combination of estrogen and PTH has also been tested in many clinical trials showing the combination therapy is more effective in increasing BMD when compared to mono-therapy with either the estrogen or PTH. In very severe osteoporotic patients, combination therapy with PTH and denosumab or PTH followed by combination treatment with denosumab or a potent bisphosphonate (i.e.; Zoledronic acid) should be considered to maximize early increase in BMD [36]. In combination of two antiresorptive agents, bisphosphonates and estrogen or bisphosphonates and SERMs are other options that have been analyzed by researchers for combination therapy [37]. There is a big concern about the combination therapy (especially combination of two antiresorptive agents) which is a oversuppression of bone remodeling calling “frozen bone”. This matter could result in a paradoxical increase in bone fragility or impairment of bone healing after a fracture [38].

More studies are needed to explore the exact anatomical areas by which anabolic and anti-catabolic agents promote bone formation and increase BMD. In general, although combination therapy has its own limitations which can be due to the cost, increased risk of frozen bone, and lack of long-term safety, it may be helpful in patients who mono-therapy failed to treat their osteoporosis. As a guideline for the clinicians, it is suggested that regular physical exercise and a proper diet/supplementation should be considered along with medical mono/combination therapy in order to get the best results.

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