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OSTEOPOROSIS: A REVIEW ON TREATMENT AND SCREENING

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ABSTRACT
Osteoporosis defined as the reduction of bone mass leading to increased fracture risk, is a major health problem. Osteoporosis mainly occurs in postmenopausal women and elderly men Although common, osteoporosis can be clinically silent, and without prevention and screening, the costs of osteoporotic fracture–related morbidity and mortality will burden the healthcare system. This is a particularly relevant concern in the context of diminishing health care resources. Cost-effectiveness analyses support early detection and treatment of high-risk patients with anti-resorptive medications such as bisphosphonates. Moreover, optimization of bone health throughout life can help prevent osteoporosis. Current guidelines recommend screening women by age 65 years, but because no guidelines for screening intervals exist, decisions are made on the basis of clinical judgment alone. Although the recent literature provides some guidance, this review further explores current recommendations in light of newer evidence to provide more clarity on prevention, screening, and management strategies for patients with osteoporosis in the primary care setting.

INTRODUCTION
Osteoporosis is a world-wide disease characterized by reduction of bone mass and change in bone architecture resulting in increased bone fragility and fracture risk.[1-4] The event of osteoporosis is expected to increase significantly in the future because of aging of the population.[5,6] Osteoporosis mainly occurs in postmenopausal women and elderly men.[7] Approximately 200 million people suffer from osteoporosis and approximately 8.9 million fractures are occurred by osteoporotic fracture.[6] These fractures found at hip, vertebrae, and distal forearm and are associated with significant morbidity, mortality, and reduced quality of life, attributed not only to the fracture itself but also to the high prevalence of co-morbidities in this population of patients.[6,7] According to the National Institutes of Health Consensus Development Panel on Osteoporosis' it is defined as "a skeletal disorder characterized by compromised bone strength leading to an increased risk of fracture." Moreover, according to the World Health Organization (WHO) criteria, osteoporosis is defined as a bone mineral density (BMD) that lies 2.5 standard deviation (SD) or more below the average value for young healthy women (a T-score of < _ 2.5 SD).[8] Osteoporosis is divided into primary osteoporosis, which is postmenopausal osteoporosis (type I) and senile osteoporosis (type II), and secondary osteoporosis, which has a clearly definable etiologic mechanism such as mal-absorption, medications such as glucocorticoids, and some diseases such as hyperparathyroidism.[9,10] Causes of osteoporosis involve increasing age, postmenopausal, hypogonadism or premature ovarian failure, low bone mass index, ethnic background (white persons are at higher risk than black persons), rheumatoid arthritis (RA), low BMD, vitamin D deficiency, low calcium intake, hyperkyphosis, current smoking, alcohol abuse, immobilization, and long-termuse of certainmedications, such as glucocorticoids, anticoagulants, anticonvulsants, aromatase inhibitors, cancer chemotherapeutic drugs, and gonadotropin-releasing hormone agonists.[11,12]

Treatment
Treatment is strictly related to severity of pathology. It is important to prevent fractures with an active lifestyle and nutritional supplements, including calcium and vitamin D intake, stopping smoking, and avoiding alcohol consumption.[13,14]

Depending on bone density, several pharmacological treatments is given for increasing bone mass and strength by inhibiting bone resorption or promoting bone formation.[15] Surgical treatments such as vertebroplasty and kyphoplasty have been used for pain relief, but their benefits are still unknown.[16]

Calcium or Vitamin D
Supplementation with calcium and vitamin D has a significant role in osteoporosis management, but not in fracture risk. The dietary vitamin D intake is based on benefits of the combination of calcium and vitamin D to

skeletal health; there is no evidence supporting a benefit of vitamin D supplementation alone, but data has shown the use in the prevention and treatment of glucocorticoid-induced osteoporosis.[17]

Bisphosphonates

Oral bisphosphonates are affordable and long-term safety data available for most compounds. They are considered first-line pharmacological therapy for post-menopausal women at high risk for fracture.[18] Bisphosphonates act by interfering with specific intracellular pathways in osteoclasts, resulting in cellular toxicity. They binds to hydroxyapatite thus absorbed by bone, inhibiting osteoclastic bone resorption.[19] Bisphosphonates are of two classes: nitrogen-containing bisphosphonates (NBPs; e.g., alendronate, ibandronate, pamidronate, risedronate, and zoledronate), which are the most common, and non-nitrogen-containing bisphosphonates (NNBPs; e.g., etidronate). NBPs inhibit the mevalonate pathway, a fundamental metabolic pathway involved in osteoclast formation and function.[20]

The first therapy is usually an oral dose of alendronate or risedronate taken once a week on an empty stomach. After administration, the patient should stand upright for at least 30–60 min and refrain from consuming food, drink, medications, or supplements for at least 30 min by this gastrointestinal adverse events are minimized.[19]

The most common adverse events, for oral bisphosphonates, are Barrett's esophagus and gastrointestinal disturbances such as dyspepsia, esophagitis, and esophageal varices. Rarely, atrial fibrillation and renal failure may occur. Therefore, intravascular bisphosphonates should not be used in patients with chronic kidney disease and an estimated glomerular filtration rate < 30–35 mL/min. Moreover, atypical femur fractures, especially subtrochanteric and diaphyseal fractures have been linked to bisphosphonate use, likely due to over-suppression of bone turnover.[18]

Denosumab

Denosumab is the first fully human monoclonal antibody that binds specifically to human RANKL to inhibit osteoclast formation and activation, thus inhibiting bone resorption. Indeed, this inhibition stops the process of bone erosion and loss.[21] Denosumab was approved for the treatment of post-menopausal osteoporosis because it reduces spine and hip fractures.[22] But it is not used as a first-line treatment, it can be used as a first-line pharmacological treatment in certain patients who are intolerant to oral bisphosphonates or who have renal failure, a serious contraindication for bisphosphonate therapy that can lead to toxicity due to lack of renal clearance of the drug. The beneficial effects of denosumab are not observed until 1 month after initiation of therapy and its anti-resorptive effects last only 4–6 months, thereby providing a margin of safety in terms of total suppression of remodeling. Similar to bisphosphonates, hypocalcemia and vitamin D deficiency should be managed before starting and during treatment with denosumab.[18] In clinical trials, denosumab was well-tolerated and did not cause jaw osteonecrosis, arterial fibrillation, or symptomatic hypocalcemia.

Denosumab should be used only in select patients. It is not recommended for premenopausal women or children, or as preventive therapy for osteoporosis; it should not be used in combination with other pharmacological agents for osteoporosis. Because denosumab inhibits the binding of RANKL to RANK, which is expressed on T-lymphocytes, B-lymphocytes, and dendritic cells in addition to pre-osteoclasts, an increased risk for infection has been reported as an adverse event of denosumab in several studies. Specifically, more frequent episodes of urinary tract infections in first-year kidney transplant recipients have been reported.[23] Therefore, antibiotic prophylaxis may be considered in patients with past recurrent infections, and patients should be instructed to report any signs of infection for appropriate treatment.

Estrogen Replacement and Selective Estrogen Receptor Modulators

Because of the roles estrogen receptor α and estrogen receptor β play in osteoclast apoptosis, the use of estrogen replacement therapy or estrogenprogestin (hormone) replacement therapy with tibolone is effective for prevention of osteoporosis in post-menopausal women. Many studies show changes in lumbar spine, total hip, and femoral neck BMD; specifically, treatment with hormone replacement therapy increases bone density at the lumbar spine and reduced bone turnover markers at 2 years treatment.[24] Because of a potential increased risk for venous thromboembolic disorders, breast cancer, cardiac events, stroke, and endometrial cancer, estrogen replacement is not recommended as first-line preventive treatment for osteoporosis and when it is initiated, it should be administrated at the lowest effective dose for a short period of time.[25] In fact, it has been reported that many women who abruptly stopped hormone replacement therapy were at a greater risk for incurring osteoporotic fractures.[26]

Selective estrogen receptor modulators are non-steroidal synthetic drugs with similar effects on bone and the cardiovascular system as estrogen, but without any of the adverse events on breast and endometrium. The most frequently used selective estrogen receptor modulators for the prevention of osteoporosis in post-menopausal women are raloxifene, lasofoxifene, and bazedoxifene, a recently FDA-approved drug. These drugs are typically used in combination with conjugated estrogens.[27] Selective estrogen receptor modulators reduce vertebral fractures in osteoporotic women by increasing trabecular bone mass in the axial skeleton, but there is no statistically significant data demonstrating that they decrease the risk for non-vertebral or hip fractures compared to placebo. Furthermore, raloxifene was shown to increase cortical porosity.[28] Selective estrogen

receptor modulators are effective in the prevention and treatment of breast cancer in premenopausal women, but increase the rates of stroke, thromboembolism, leg cramps, and vasomotor symptoms in post-menopausal women.[25] For this reason, they are contraindicated for prevention or treatment of osteoporosis in premenopausal women, but they are suggested as first-line therapy for the prevention of osteoporosis in post-menopausal women.

Calcitonin

Calcitonin inhibits bone resorption by increasing osteoblast activity. Until recently, calcitonin was considered a second line therapy for osteoporosis in settings where first-line drugs were intolerable or did not elicit a therapeutic response. To date, data on the effect of calcitonin on BMD of other skeletal sites are conflicting, as shown in recent studies. Calcitonin is available in injectable and intranasal; oral formulations, which are more convenient than other administration modalities, are in development.[29] Women treated with calcitonin experience an increase in lumbar spine BMD and a decrease in biomarkers of bone turnover, especially women taking the oral formulation; however, calcitonin does not prevent new vertebral, non-vertebral, or hip fractures. Similarly, a recent major clinical trial failed to show that calcitonin is efficacious in preventing fractures.[30]

Teriparatide

Teriparatide it is a recombinant human parathyroid hormone, namely a peptide of PTH. It is the first, and currently the only, approved anabolic agent for the treatment of osteoporosis that stimulates osteoblastic bone formation to improve bone quality and bone mass.[31] It activates osteoblasts by binding to PTH/PTHrP type 1 receptor, directly stimulating bone formation on active remodeling sites and on previously inactive bone surfaces, and initiating new remodeling sites. Several studies have shown a rapid rise in biochemical markers of bone formation during the first months of teriparatide treatment without an accompanying increase in bone resorption. Therefore, it stands to reason that in the early stages of treatment, bone formation exceeds bone resorption. Teriparatide causes an increase in bone density that is clearly observed on dual-energy x-ray absorptiometry, especially in the lumbar spine and femoral neck, where BMD values increase significantly, reducing fracture risk, as shown after 24 months of treatment, which is the total treatment duration approved for patients with osteoporosis at high risk for fracture.

Strontium Ranelate

Strontium ranelate is an anti-resorptive agent approved in Europe for the treatment of men and post-menopausal women with severe osteoporosis who cannot tolerate other pharmacological agents. The mechanism of action is not entirely clear, but a modest antiresorptive effect has been noted, resulting from inhibition of osteoclast function and promotion of osteoblast differentiation and proliferation through the calcium sensing receptor (CaSR). This results in increased BMD, although this is not strictly related to a large reduction in fracture risk.[32] Common adverse events are cardiovascular events, venous thromboembolism, myocardial infarction, gastrointestinal discomfort, and signs and symptoms of nervous system disorders, such as headache, seizure, and memory loss. A rarely reported adverse event is allergic reactions, such as drug rash with eosinophilia and systemic symptoms (DRESS syndrome).[33-35] Because of the high risk for heart injuries, strontium ranelate is now considered a second line treatment for osteoporosis, only used when other medications for osteoporosis are unsuitable, in the absence of contraindications. Additional measures, including restrictions in patients with heart or circulatory problems, are also recommended to minimize the cardiovascular risks. The use of strontium ranelate alone or in combination for the treatment of osteoporosis has several limitations because of its potential adverse events when used long-term, but represents a valid available option for treating osteoporosis in selected patients.

Screening

Osteoporosis screening is based on BMD measurement, usually by DXA, which is then used to predict fracture risk.[36,37] The benefits includes in noninvasive nature, low level of radiation exposure, and short test time. The disadvantages include the inability to accurately compare results from one center to bone architecture.[38] The multiple organizations have developed evidence based osteoporosis screening. Although no randomized controlled studies have demonstrated that screening effects fracture outcome.[38] Several studies indicated that low BMD predicts fracture screening intervals.[39,40] In 2007 a prospective occurrence and numerous randomized controlled studies demonstrate that treatment of osteoporosis significantly reduces fracture risk.[41] Most guidelines recommend initiating screening of post menopausal women by age 65 with more risk factors however the later it's difficult to identify clearly.[40,41]

The guideline has not been issued about screening intervals due to insufficient data. The USPSTF suggests a minimum of 2 years between screenings to reliably measure BMD change because of limitations in test precision.[42] There is only three published studies have tried to identify appropriate cohort study was conducted to determine whether repeated BMD screening measurement aided fracture risk prediction beyond the initial measurement. They studied 4,124 women aged 65 years and older reported that in healthy, postmenopausal women, BMD measurement by using fracture as the outcome metric.[43]

A 2012 study investigated how BMD testing interval related to osteoporosis development before fracture occurrence. The investigators studied 4,957 women aged 67 years and older for up to 15 years patients had

baseline normal BMD. The objective was to estimate the interval needed for osteoporosis development in 10% of the subjects. Estimates were adjusted for major clinical risk factors such as smoking, glucocorticoids use and rheumatoid arthritis.[44] For women with normal BMD or mild osteopenia developed by 15 years. Based on the study, the key determinant of the BMD interval appears to be baseline T score. For those with initial normal BMD or mild osteopenia the screening interval could be 15years. For women with moderate osteopenia, screening should likely be performed yearly. Notably the estimated time to osteoporosis decreased with increasing age. These were the first evidence based estimates for optimal screening intervals before the development of osteoporotic fractures and before initiation of treatment for older postmenopausal women.[45,46]

CONCLUSION

Treatment of osteoporosis is important for the well being of older patients and also to reduce the risk of fractures. Early diagnosis will help in the treatment with currently available anti-osteoporotic drug. Calcium, vitamin D and oral bisphosphonates are first line therapy as well as cost effective. To increase BMD, suppress bone remodeling, prevent fractures the newer second or third line drugs such as teriparatide, denosumab and raloxifene are used. Osteoporosis treatment reduces fracture risk and is recommended after hip or vertebral fracture for patients with a T-score that is - 2.5 or more negative at the femoral neck or spine without secondary causes. Treatment also is recommended for patients with a FRAX 10-year risk of at least 3% for hip fracture or at least 20% for major osteoporotic fracture with osteopenia A recent model suggests that initiating screening at age 55 in postmenopausal women may be more cost-effective than current USPSTF guidelines. The most important factors for determining optimal screening intervals appear to be T-score and age. For older postmenopausal women with normal BMD or mild osteopenia at baseline, clinicians may wait up to 15 years before repeat screening. Older postmenopausal women with moderate osteopenia at baseline can be screened every 5 years, and those with advanced osteopenia likely should be screened yearly.

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