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MANAGEMENT OF OSTEOPOROSIS IN FAMILY PRACTICE

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Abstract:

Introduction: *The important target when managing females with post-menopausal osteoporosis is to avoid the development of future pathological fractures. Thus, detecting females at the highest risk is a priority. Low bone mineral density, especially at the site of the hip, is an important risk factor for the development of pathological fractures: for every 1-SD decrement in bone mineral density, the risk of developing a pathological fracture increases by a factor of two to three,6 therefore, most protocols suggest a single bone mineral density evaluation at or around sixty-five years of age. On the other hand, a more comprehensive evaluation of clinical predisposing factors is beneficial to help define the absolute risk for an individual and to detect patients who require management. The Fracture Risk Assessment Tool (FRAX), that was created by the WHO based on data acquired from several international cohort studies, incorporates established risk factors and bone mineral density at the site of the femoral neck to predict individual ten-year risk of developing a hip or another major osteoporotic fracture; in addition, its main use is encouraged by multiple international professional organizations.*

Aim of work: *In this review, we will discuss osteoporosis*

Methodology: *We did a systematic search for osteoporosis using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.*

Conclusions: *Females who have a low bone mineral density and a history of pathological fractures are consistent with having osteoporosis. It is recommended for these females to increase physical exercise, avoid smoking and alcohol abuse, and consume a total calcium intake of 1000 to 1500 milli-gram daily and a total vitamin D intake of 600 to 800 IU daily, along with the administration of an anti-resorptive medication. It is also generally recommended to prescribe a bisphosphonate as a first-line treatment if there are no clear contraindications; with a thorough discussion with the patient about the rare possible risks of developing atypical femur fracture or jaw osteonecrosis but also the higher anticipated effects in terms of overall decrease in the rates of developing pathological fractures. Based on the results of follow-up bone mineral density measurement, it is also recommended to discuss the possibility of temporarily stopping the bisphosphonate after five years of treatment.*

Key words: *osteoporosis, overview, presentation, causes, management.*

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INTRODUCTION:

The important target when managing females with post-menopausal osteoporosis is to avoid the development of future pathological fractures. Thus, detecting females at the highest risk is a priority. Low bone mineral density, especially at the site of the hip, is an important risk factor for the development of pathological fractures: for every 1-SD decrement in bone mineral density, the risk of developing a pathological fracture increases by a factor of two to three,6 therefore, most protocols suggest a single bone mineral density evaluation at or around sixty-five years of age. On the other hand, a more comprehensive evaluation of clinical predisposing factors is beneficial to help define the absolute risk for an individual and to detect patients who require management. The Fracture Risk Assessment Tool (FRAX), that was created by the WHO based on data acquired from several international cohort studies, incorporates established risk factors and bone mineral density at the site of the femoral neck to predict individual ten-year risk of developing a hip or another major osteoporotic fracture; in addition, its main use is encouraged by multiple international professional organizations. [1]

In this review, we will discuss the most recent evidence regarding osteoporosis.

METHODOLOGY:

We did a systematic search for osteoporosis using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.
The terms used in the search were: osteoporosis, overview, presentation, causes, management.

Overview

Females who acquired a recent osteoporotic pathological fracture are specifically at a high risk for developing an additional pathological fracture. A strategy for detecting these individuals is the use of a fracture liaison service aimed for patients with recent pathological fractures that gives consultative approach with advice and recommendations for the physician regarding the diagnosis and management; this service has been proven to be highly cost-effective. [2] Other high-risk individuals are those who have secondary osteoporosis due to an underlying hyperparathyroidism, malabsorption, multiple myeloma, diabetes mellitus (with the presence or absence of low bone mineral density), or inflammatory bowel disease. In individuals who have low bone mineral density or a previous pathological fracture or those individuals who are being considered for anti-osteoporosis treatment, a single assessment for the current status vitamin D is generally recommended, even in those individuals who receive exogenous vitamin D supplements. [3]

Management with Nonpharmacologic Options:

Physical exercise and Modifiable Risk Factors Resistance could potentially improve muscle mass and can temporary increase bone mineral density. [4] despite that data from randomized studies are not able to prove that weight-bearing physical exercise decreases the risk of developing fractures, large longitudinal studies that involved high-resolution computed tomography have demonstrated improvements on skeletal microarchitecture in correlation with some forms of regular physical exercise. [5] pathological fractures usually result following falls, and the frequency of falls and the proportion of falls that cause fractures are more with increasing age. Physical activity and balance programs (like yoga and tai chi) might cause improved balance and an improvement in muscle tone and might also decrease the frequency of falls among some elderly individuals. Besides physical activity, evaluation of the house for the presence of any hazards, cessation of psychotropic medications (if possible), and initiating the use of a multidisciplinary protocol to evaluate predisposing factors are important strategies for possibly decreasing the frequency of falls. Other protocol could include counseling about cigarette smoking (which is associated with decreased bone mineral density) and about alcohol abuse (that is known to increase the frequency of falls).

Calcium and Vitamin D

The benefits of calcium and vitamin D supplements for preventing osteoporotic pathological fractures is an area of debate. [6] In a large randomized study that was conducted by the Women's Health Initiative (WHI) investigators including more than thirty-six thousand post-menopausal females, calcium (1000 milli-gram of elemental calcium supplementation daily) plus vitamin D (400 international-unit everyday) was not associated with a statistically significant impact on the risk of acquiring pathological fractures, despite that there was an evidence of benefits in a post hoc subgroup analysis that was done on females who were sixty years of age or older and among females who were compliant to their assigned regimens. [7] later meta-analyses of several large studies of both calcium and vitamin D treatment have proven the presence of a small decline in pathological fractures frequency, especially among the institutionalized elderly individuals or those who

have a relatively low intake of calcium supplements or vitamin D supplements. [8] on the other hand, vitamin D treatment alone has not been proven to decrease the frequency of developing a pathological fracture or increase bone mineral density, despite that smaller studies have claimed that daily supplementation (but not intermittent high-dose supplementation) might mildly decrease the frequency of falls.16 studies of supplemental calcium alone have been too small to conclude the effects on frequency of pathological fractures. In the WHI trial, females who were assigned to treatment with calcium with vitamin D had a seventeen percent higher chance of developing kidney stones when compared to females who were assigned to placebo, most likely due to the high intake of calcium at baseline (approximately 1150 milli-gram daily in each group). Standard guidelines for most post-menopausal females who have osteoporosis recommend a total calcium intake of one thousand milli-gram daily (through diet, exogenous supplements, or both) and a total vitamin D intake of six hundred international unit per day.

Pharmacologic Therapies

Pharmacologic drugs for the management of osteoporosis could be categorized as either anti-resorptive (these target the osteoclast-mediated bone resorption) or anabolic (these stimulate osteoblasts to form new bone). Medications of each of those types shave been proven to benefit bone mineral density and decrease the frequency of developing a pathological fracture.

Estrogen therapy, either with or without progesterone therapy, has a direct impact on the osteocytes, the osteoclasts, and the osteoblasts, causing the inhibition of bone resorption and the maintenance of bone formation. In the WHI study, estrogen treatment significantly decreased the frequency of developing new vertebral, non-vertebral, and/or hip fractures. [9] Both low-dose conjugated estrogens and ultra-low-dose estradiol, that are usually used in the short-term treatment for post-menopausal clinical manifestations, improve bone mineral density, but their anti-fracture role has not been proven. [10]

Concerns regarding non-skeletal complications linked to the use of estrogen (including breast cancer and coronary, cerebrovascular, and/or thrombotic events) have caused the release of several recommendations against the use of estrogen as a first-choice for individuals with osteoporosis.

Selective estrogen-receptor modulators (SERMs), on the other hand, stimulate specific tissue receptors for estrogen. Raloxifene, for example, is a Selective estrogen-receptor modulator that has been approved to manage osteoporosis; it blocks bone resorption, improves spine bone mineral density mildly, and reduces the frequency of developing vertebral pathological fractures by about thirty percent. However, it has no effect on nonvertebral or hip pathological fractures. the long-term use of raloxifene reduces the risk of developing breast-cancer among high-risk females but elevates the risk of developing thromboembolic events. [11]

More recently, the use of a combination of another Selective estrogen-receptor modulator 'bazedoxifene', along with estrogen received the approval for the management of menopausal manifestations and to avoid the development of osteoporosis but not for the management of osteoporosis.

Bisphosphonates block bone remodeling. Several oral and IV bisphosphonates have been proven in randomized studies to decrease the risk of developing a pathological fracture. [12] bisphosphonates as a class of drugs represent the majority of drugs prescribed for the management of osteoporosis and are all currently available in generic form. Despite that data from randomized studies and clinical trials show that they are usually safe, hypocalcemia and mild muscle pain can occur sometimes. Two rare but serious adverse events have also been reported. These are the development of atypical femoral fractures (like fractures in the subtrochanteric region that have a transverse orientation and noncomminuted morphologic features, show focal lateral cortical thickening, occur with minimal trauma, and might be bilateral) [13] and jaw osteonecrosis, that is known as the development of exposed bone in the maxillofacial region that does not heal within eight weeks.

The use of bisphosphonates must be limited to individuals who have a creatinine clearance that is higher than thirty-five milli-liters per minute and normal levels of serum vitamin D; symptomatic hypocalcemia may occur in individuals who have low 25-hydroxyvitamin D levels and who concomitantly receive treatment with bisphosphonates.

All oral bisphosphonates have been examined in several large, placebo-controlled, randomized studies with pathological fracture end points, among females who were receiving calcium and vitamin D along with daily doses of the bisphosphonates. Oral bisphosphonates are currently used in weekly doses (alendronate with risedronate) or monthly doses

(ibandronate with risedronate); comparability with every day dosing has been demonstrated by evaluation of comparative changes in bone mineral density and bone-turnover markers.

Minor irritation of the digestive tract might happen following the initiation of oral bisphosphonates treatment and could be decreased by adherence to careful dosing instructions. Oral bisphosphonates must not be prescribed for individuals who suffer from clinically significant esophageal diseases like achalasia. In the two Fracture Intervention Trials (FIT) of alendronate, that were paired randomized studies (with three to four years of follow-up) involving post-menopausal females with a bone mineral density T score of −1.6 or less at the femoral neck, [14] the frequency of vertebral pathological fractures was significantly less (by about fifty percent) among those who received alendronate (at a dose of five milli-gram daily for the first two years, followed by ten milli-gram daily) than among those individuals who received placebo therapy. In the first study (that involved females with existing spinal fractures), the frequency of developing hip pathological fractures was significantly less by about fifty-one percent with alendronate, and the frequency of non-vertebral pathological fractures was twenty percent lower with alendronate than with placebo therapy (with a p value of .06).26 In the second study (that involved females with no existing vertebral pathological fractures), the frequency of developing hip and/or non-vertebral pathological fractures were not significantly less with alendronate treatment than with placebo therapy overall27 but were significantly less (non-vertebral pathological fractures by thirty-five percent and hip pathological fractures by fifty-six percent) in a pre-specified sub-group analysis of females with a bone mineral density T score of −2.5 or less at the hip. [15]

Two randomized, controlled studies of risedronate (five milli-gram per day) in post-menopausal females with existing vertebral pathological fractures, decreased bone mineral density in the spine, or both demonstrated that over a period of three years, the risk of developing vertebral pathological fractures was less (by forty-one to forty-nine percent) with risedronate than with placebo therapy, as was the frequency of osteoporotic non-vertebral pathological fractures (by thirty-three to forty percent). A larger study with a hip-fracture end point of risedronate (2.5 or five milli-gram daily) that involved females aged seventy years or older who were at high risk for developing hip pathological fractures demonstrated a thirty percent lower rate of such fractures over a period of three years with risedronate than with placebo therapy. A study of ibandronate (2.5 milli-gram daily) demonstrated a sixty-two percent less rate of vertebral pathological fractures with ibandronate than with placebo treatment but no decrease in the frequency of non-vertebral pathological fractures over a period of three years, although a post-hoc sub-group analysis of females with T scores less than −3.0 demonstrated significantly less non-vertebral pathological fractures with the use of ibandronate than with the use placebo. Ibandronate is also available in an IV formulation.

Compliance to oral bisphosphonates is not high, and it is though that less than forty percent of individuals who are prescribed oral drugs are still taking them after one year. IV bisphosphonates (like ibandronate and zoledronic acid) are other alternatives that do not need frequent use. In a large randomized study that involved females
with relatively low bone mineral density, existing vertebral pathological fractures, or both,35 a once-per-year infusion (for more than 15 minutes) of five milli-gram of zoledronic acid led to significantly decreased frequencies of vertebral pathological fractures (by seventy percent), hip pathological fractures (by forty-one percent), and non-vertebral pathological fractures (by twenty-five percent) than the rates with placebo therapy. In another study that involved females and males who were randomly assigned to receive treatment with zoledronic acid or placebo within ninety days following surgical repair of a hip pathological fracture, those who received treatment with zoledronic acid had a significantly less rates of developing subsequent pathological fractures (by thirty-five percent).36 Zoledronic acid leads to an acute-phase reaction (flu-like symptoms) for up to three days after the first infusion in up to one

third of patients (and only rarely after later infusions) [16]; co-administration of paracetamol decreases both the frequency of developing this reaction (by about the half) and the severity of clinical manifestations. a higher frequency of atrial fibrillation has been detected in some studies but not in all of them.

Denosumab

Denosumab was the first biological agent that was approved to treat patients with osteoporosis. Its action is totally different from that of bisphosphonates: it blocks bone resorption by binding to the receptor activator of nuclear factor ligand (RANKL), therefore reducing the differentiation of osteoclasts. In contrast to bisphosphonates, it could be used in females with

poor renal function. A large study that involved females with a bone mineral density T score below −2.5 but not below −4.0 at the lumbar spine or total hip demonstrated that denosumab therapy (sixty milli-gram given two times per year through subcutaneous injection) caused a significantly less risk of developing vertebral pathological fractures (by sixty-eight percent), hip pathological fractures (by forty percent), and non-vertebral pathological fractures (by twenty percent) than the frequency with placebo. [17] similar to bisphosphonates, rare cases of atypical femur fractures and jaw osteonecrosis have been reported in patients who were on denosumab therapy.

Teriparatide

Teriparatide medication is an anabolic drug that acts mainly by improving bone formation instead of reducing bone resorption. In a twenty-one-month study that involved females with low bone mineral density and previous vertebral pathological fractures, teriparatide (20 micro-grams daily) was correlated with a reduced risk of developing vertebral pathological fractures (by sixty-five percent) and non-vertebral pathological fractures (by thirty-five percent) than the risk with placebo therapy, but not with a reduced risk of developing hip pathological fractures. [18] Teriparatide is usually administered by every day self-injection and is approved for up to two years of use. Trials of its administration after treatment with bisphosphonate have demonstrated that it retains its anabolic properties, although its effects are mildly blunted. After teriparatide is stopped, its effects are rapidly lost, so it must be followed by an anti-resorptive agent.

There is a black-box warning regarding a risk of developing osteosarcoma linked with teriparatide therapy, based on trials of long-term, high-dose teriparatide in rodents, however, to our knowledge only one reported case has been documented in more than one million human users.

Areas of Uncertainty

The relative importance of the two rare adverse events (atypical fractures and jaw osteonecrosis) versus the observed benefits of using anti-resorptive therapy is not certain and remains an area of debates. The concerns of many females regarding these potential adverse events have increasingly become a crucial barrier to start anti-osteoporosis treatment and to treatment compliance.

Atypical fractures have been reported in rare cases in females using bisphosphonates and denosumab. Their pathological mechanisms are not clear. Case-control and cohort studies and analysis of a multiple randomized studies [19] have evaluated the association between atypical femoral fractures and osteoporosis therapy (mainly bisphosphonate medications); in all the studies, the rate of these fractures is relatively low, ranging from approximately one in 100,000 to five in 10,000 among users of bisphosphonate. The rate of jaw osteonecrosis of the jaw is also very low (estimated at less than one case per 10,000 of users of bisphosphonate).

CONCLUSIONS:

Females who have a low bone mineral density and a history of pathological fractures are consistent with having osteoporosis. It is recommended for these females to increase physical exercise, avoid smoking and alcohol abuse, and consume a total calcium intake of 1000 to 1500 milli-gram daily and a total vitamin D intake of 600 to 800 IU daily, along with the administration of an anti-resorptive medication. It is also generally recommended to prescribe a bisphosphonate as a first-line treatment if there are no clear contraindications; with a thorough discussion with the patient about the rare possible risks of developing atypical femur fracture or jaw osteonecrosis but also the higher anticipated effects in terms of overall decrease in the rates of developing pathological fractures. Based on the results of follow-up bone mineral density measurement, it is also recommended to discuss the possibility of temporarily stopping the bisphosphonate after five years of treatment.

REFERENCES:

1. **Osteoporosis prevention, diagnosis, and therapy.2000** NIH Consens Statement 2000; 17: 1-45.
2. **Yates CJ, Chauchard MA, Liew D, Bucknill A, Wark JD.2015** Bridging the osteoporosis treatment gap: performance and cost-effectiveness of a fracture liaison service. J Clin Densitom 2015; 18: 150-6.
3. **Amin S, Achenbach SJ, Atkinson EJ, Khosla S, Melton LJ III.2014** Trends in fracture incidence: a population-based study over 20 years. J Bone Miner Res 2014; 29: 581-9.
4. **Hinton PS, Nigh P, Thyfault J.2015** Effectiveness of resistance training or jumping-exercise to increase bone mineral density in men with low bone mass: a 12-month randomized, clinical trial. Bone 2015; 79: 203-12.
5. **Evans RK, Negus CH, Centi AJ, Spiering BA,**

Kraemer WJ, Nindl BC.2012 Peripheral QCT sector analysis reveals early exerciseinduced increases in tibial bone mineral density. J Musculoskelet Neuronal Interact 2012; 12: 155-64.

6. **Bauer DC.**2013 Calcium supplements and fracture prevention. N Engl J Med 2013; 369: 1537-43.
7. **Jackson RD, LaCroix AZ, Gass M, et al.2006** Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006; 354: 669-83.
8. **Murad MH, Drake MT, Mullan RJ, et al.**2012 Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network metaanalysis. J Clin Endocrinol Metab 2012; 97: 1871-80.
9. **Jackson RD, Wactawski-Wende J, LaCroix AZ, et al.2006** Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. J Bone Miner Res 2006; 21: 817-28.
10. **Richman S, Edusa V, Fadiel A, Naftolin F.2006** Low-dose estrogen therapy for prevention of osteoporosis: working our way back to monotherapy. Menopause 2006; 13: 148-55.
11. **Cummings SR, Tice JA, Bauer S, et al.** Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. J Natl Cancer Inst 2009; 101: 384-98.
12. **Crandall CJ, Newberry SJ, Diamant A, et al.2014** Comparative effectiveness of pharmacologic treatments to prevent fractures: an updated systematic review. Ann Intern Med 2014; 161: 711-23.
13. **Shane E, Burr D, Abrahamsen B, et al.2014** Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2014; 29: 1-23.
14. **Black DM, Cummings SR, Karpf DB, et al.1996** Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996; 348: 1535-41.
15. **Cummings SR, Black DM, Thompson DE, et al.1998** Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998; 280: 2077-82.
16. **Reid IR, Gamble GD, Mesenbrink P, Lakatos P, Black DM.2010** Characterization of and risk factors for the acute-phase response after zoledronic acid. J Clin Endocrinol Metab 2010; 95: 4380-7.
17. **Cummings SR, San Martin J, McClung MR, et al.2009** Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009; 361: 756- 65.
18. **Neer RM, Arnaud CD, Zanchetta JR, et al.**2001 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.
19. **Black DM, Kelly MP, Genant HK, et al.2010** Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. N Engl J Med 2010; 362: 1761-71.