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Controversies in Osteoporosis Management: How Do You Treat a Newly Menopausal Woman With Low Bone Mass: When and How Is It Appropriate to Provide Pharmacologic Intervention to Prevent Osteoporosis?

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Introduction

Bone loss begins after the age of 30, the time on average when peak bone mass (PBM) is achieved.[1] The period of most rapid bone loss in women begins 1 year before the final menses and lasts approximately 3 years, during which time there is a 6% and 7% bone loss at the femoral neck and lumbar spine, respectively.[2] As bone microarchitectural changes associated with bone loss are largely irreversible, treatment is unlikely to fully restore the bone strength and quality. The main strategy for prevention of osteoporosis or low bone mass (LBM), therefore, consists of 2 primary approaches: maximizing PBM and minimizing the rate of bone loss. For newly menopausal women with LBM, it is too late to initiate the first approach if their PBM was not optimally achieved; therefore, they may be at higher risk of developing osteoporosis after menopause, even with a typical rate of bone loss (0.5% to 1.5% per year).[3]

Although women with osteoporosis (T-scores ≤ -2.5) are at a higher risk of fracture than those with LBM (T-score between -2.5 and -1), the absolute number of fractures is greater in women with LBM because this population is much larger.[4] Therefore, an essential step for the prevention of osteoporotic fractures is to diagnose menopausal women with LBM. How can we identify newly menopausal women with LBM, who may benefit from pharmacological intervention? Routine or baseline screening of younger postmenopausal women is not recommended,[5] unless any of the following risk factors are noted[4,6]: history of a fragility fracture, weight < 127 lb, medical causes of bone loss, parental history of a hip fracture, current smokers, alcoholism, or rheumatoid arthritis.

The fracture risk assessment tool (FRAX),[7] which was developed in collaboration with the World Health Organization to predict the risk of an osteoporotic fracture in the next 10 years, can be used in newly menopausal women to determine whether a dual-energy x-ray absorptiometry scan should be recommended.[8] In this regard, the risk factors without a femoral neck T-score can be used to calculate this result. A FRAX 10-year risk of a major osteoporotic fracture of 9.3%, which is equivalent to the risk of fracture found in a 65-year-old white women with no risk factors, justifies the need for a dual-energy x-ray absorptiometry scan in women younger than 65 years of age.[5]

One is never too old to make lifestyle changes to prevent bone loss. Nonpharmacological interventions, such as diet, exercise, and smoking cessation, are recommended for all ages to improve bone health and prevent bone loss. This important intervention needs to be reiterated for newly menopausal women, especially after detecting LBM or osteoporosis. Pharmacologic interventions are associated with increased costs and potential side effects, and hence, only select patients are candidates for preventive pharmacotherapy. When to recommend a specific agent to younger postmenopausal women with LBM is a practical but controversial medical decision.

For a newly menopausal woman who has the diagnosis of LBM (osteopenia) or is concerned about her bone health, even with a normal bone mineral density (BMD), the FRAX calculator can be used to assist health care providers determine whether a pharmacologic intervention is indicated. Women with a 10-year risk of a major osteoporotic fracture $\geq 20\%$ or of a hip fracture $\geq 3\%$ by FRAX, as well as women who have had a low-impact fracture (especially of the vertebra, pelvis, or hip) in the absence of bone density criteria for osteoporosis are candidates for pharmacologic intervention. Before the initiation of a pharmacologic agent, it is essential to consider and rule out underlying medical conditions that may be a secondary cause for LBM. In a younger patient population, a full metabolic

evaluation is indicated.[6] The drugs currently approved by the Food and Drug Administration (FDA) for osteoporosis prevention are estrogen, several bisphosphonates, and raloxifene.

Estrogen

Estrogen therapy (ET), and hormonal therapy (HT), have been shown to prevent fractures.[9] Despite concerns raised with the Women's Health Initiative (WHI), with new evidence suggesting many benefits and minimal risks in newly menopausal women,[10] this therapy may gain renewed interest. Although the benefit of ET/HT for the prevention of osteoporosis is dose-related, the current guidelines suggest that ET/HT should be taken in the lowest dose for the time needed to achieve treatment goals.[11] Although HT can be used for 5 years before encountering concerns of breast cancer,[12] ET can be used for an extended period of time in the absence of other risk factors as newer evidence shows a decreased risk of breast cancer.[10] When alternate drug therapies are not feasible, extended use of HT/ET can be considered as an option.[11]

Bisphosphonates

Bisphosphonates currently approved by the FDA for prevention of postmenopausal osteoporosis are alendronate, risedronate, ibandronate, and zoledronic acid, with doses different than those used for treatment with alendronate and zoledronic acid. Because of potential complications with long-term bisphosphonate use and the subsequent loss of BMD after discontinuation, there is no consensus on the appropriate duration for the prevention of osteoporosis or the length of a "drug holiday" when used for treatment. It has been proposed, for treatment of postmenopausal osteoporosis, that patients at minimal risk of fractures could stop the treatment after 5 years and remain off as long as their BMD is stable and no fractures occur. Higher risk patients may benefit from longer treatment (10 y), and be offered a drug holiday of 1 or 2 years, and perhaps be on a non-bisphosphonate treatment during that time.[13]

Selective Estrogen Receptor Modulators

Raloxifene (60 mg/d) is the only selective estrogen receptor modulator currently approved in the United States for the prevention and treatment of postmenopausal osteoporosis. It has been shown to increase BMD in the spine and femoral neck and reduce the risk of vertebral fractures in older postmenopausal women with osteoporosis after 3 years of treatment.[14] An important nonskeletal benefit of raloxifene is the reduction of breast cancer risk found in high-risk women.[15] However, it increases the risk of hot flashes, thromboembolic events, and death from strokes (not increased risk of stroke), with no apparent effect on heart disease or endometrial hyperplasia/cancer. As newly postmenopausal woman are often concerned about the prevention of osteoporosis and the reduction of breast cancer risk, raloxifene can be an ideal option for these women who are typically at low risk for deep vein thrombosis and stroke and are excellent candidates for treatment with raloxifene, especially if they have minimal vasomotor symptoms.

Conclusions

Although early pharmacologic intervention in newly menopausal women with LBM may be more effective in reducing the risk of osteoporosis and osteoporotic fractures, compared with initiating drug therapy after osteoporosis is diagnosed, the increased cost and risks warrant

careful selection of candidates for preventive therapy. Newly menopausal women with LBM should be considered for preventive therapy based on fracture risk, as determined by a combination of BMD, clinical risk factors, and the FRAX calculator. Patients with higher risk of fracture are more likely to benefit from drug therapy. For newly menopausal women with LBM who are candidates for preventive therapy, it may be reasonable to consider raloxifene or, in a symptomatic woman, ET/HT as first-line therapeutic options. For women in their 60s, when the risk of hip fracture and thrombosis begin to increase, bisphosphonates should be more strongly considered. For women on ET/HT, as the benefit of ET/HT for bone health is dose-related, it is recognized that the lower doses currently recommended may not be as effective for fracture prevention.[8] Although there is no consensus on the duration of drug therapy and/or drug holidays, precaution and periodic reassessment of the need for continued preventive therapy should be undertaken.

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