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Clinical Review

Postmenopausal Osteoporosis: A Clinical Review

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Abstract

In postmenopausal women, osteoporotic fractures are more common than stroke, myocardial infarction, and breast cancer combined, and fractures can be costly and result in disability or death. Because there are no signs or symptoms of osteoporosis other than fracture, risk assessment is necessary to identify those at higher risk for clinical events. For women, a clinical fracture risk assessment (FRAX) is appropriate at menopause. Bone mineral density (BMD) measurement is recommended for women at age 65, and earlier for those who have risk factors. Adequate calcium, vitamin D, and weight-bearing exercise are important for bone health at all ages, and those at high risk for fracture based on BMD or FRAX should be offered medical therapy to reduce fracture risk after an appropriate medical evaluation. Bisphosphonates can accumulate in bone, so after a period of treatment, lower risk patients may be offered a period off drug therapy. However, the effects of denosumab are not sustained when treatment is discontinued, so there is no ''drug holiday'' with denosumab. Anabolic therapy can be offered to those with higher risk for fracture. Although rare safety concerns regarding atypical femoral fracture and osteonecrosis of the jaw have received prominent attention, for patients who are appropriately treated according to National Osteoporosis Foundation guidelines, the benefit of hip fracture risk reduction far outweighs the risk of these uncommon side effects. Accurate information for patients and shared decision-making are important for acceptance and persistent with appropriate treatment.

Keywords: postmenopausal, osteoporosis, fracture, bone density, bisphosphonates, denosumab

Background

Osteoporosis is officially defined as ''a skeletal disorder characterized by reduced bone strength predisposing to an increased risk of fracture.''[1] Many patients who have ''osteoporosis'' by bone density testing will not fracture and many fractures due to ''osteoporosis'' occur in patients whose bone density is better than the osteoporosis cut point.[2,3] Because fracture is the important sequela, I prefer to define the concern as ''a patient at high risk of fracture due, at least in part, to increased skeletal fragility.''[4] Considering a densitometric diagnosis of ''osteoporosis'' based on femoral neck bone mineral density (BMD) 2.5 SD or more below the young-adult mean (T-score −2.5 or below); or a hip fracture regardless of BMD; or a clinical vertebral, proximal humerus, pelvis, or distal forearm fracture with a T-score between −1.0 and −2.5; or fracture risk assessment (FRAX) score at the U.S. National Osteoporosis Foundation intervention thresholds (≥3% for hip fracture or ≥20% for major osteoporotic fracture), the prevalence of affected persons is 16.5 million in the United States, 9.2 million of whom are women—approximately 30% of women aged ≥50.[5]

Fractures can be serious, costly, and result in disability and even death. Although osteoporosis (low bone mass) can occur at any age and in both sexes, it is more common in women than men (peak bone mass is lower in women than in men and men have no universal equivalent to menopause, when there is accelerated bone loss over about a decade). Fractures are also more common in women than men, in part, because of lower bone mass and also because there is less competing mortality (women tend to live longer than men). In postmenopausal women, fractures due to osteoporosis are more common than stroke, myocardial infarction, and breast cancer combined.[6] For women aged 50, the lifetime risk of a fracture due to osteoporosis is 50%. A fracture can be a life changing event and may represent a significant threat to personal independence.

Fracture Risk Assessment

Skeletal fragility and high fracture risk can occur at any age, in any race, and either sex, but is more common in women than men and increasingly common with advancing age. A fracture with minimal or moderate trauma should lead

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to further evaluation—clearly fractures of the long bones (arms, legs), spine, and pelvis are associated with increased risk of future fractures at other locations, whereas fractures of ribs, knees, elbows, and shoulders (and fractures of fingers, toes, hands, feet, skull or face) are not. Other than fractures, there are no signs or symptoms of osteoporosis. Therefore, a FRAX is necessary to identify people at risk.

In the absence of risk factors other than sex and age, BMD measurement using dual-energy X-ray absorptiometry (DXA) is recommended for women at age 65[7]; however, a clinical FRAX should be performed around age 50 (or earlier for women who undergo premature menopause) for women with risk factors: low body weight, early menopause (before about age 45), family history of osteoporosis, diseases (*e.g.*, rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease), and drugs (*e.g.*, glucocorticoids, proton pump inhibitors, selective serotonin reuptake inhibitors) that increase fracture risk—any of these would be a reason to order a BMD assessment sooner.[8]

Fundamental Measures for Bone Health

Adequate calcium, vitamin D, weight-bearing, and resistance exercise are important for bone health at any age and likely contribute to the effectiveness of medications to reduce fracture risk. The Institute of Medicine recommends a calcium intake of 1200 mg/day, ideally from foods; calcium supplements may be needed for patients whose diets do not supply sufficient calcium. Despite a flurry of reports suggesting adverse effects of calcium supplements on cardiovascular events, most evidence supports little or no safety concerns and mild benefits.[9] For vitamin D, 600–800 IU/day is recommended for public health purposes, but a supplement of 2000 IU/day is reasonable for those at increased risk of osteoporosis; serum 25-OH D levels above 30 ng/mL may be the appropriate target in such patients.[10] Walking (or a weight-bearing ''walking equivalent'' such as treadmill or elliptical) for 30–40 minutes at least three times per week would be ideal. Tai chi, yoga, and Pilates may help to maintain or improve flexibility and balance and reduce the risk of falling.

Pharmacologic Therapy

Patients at high risk of fracture should be offered medication to reduce fracture risk. The US National Osteoporosis Foundation recommends pharmacologic treatment for patients with hip or spine fractures thought to be related to osteoporosis, those with BMD 2.5 SD or more below the young normal mean (T-score −2.5 or below), and those with BMD between 1 and 2.5 SD below the young normal mean whose 10-year risk, using an on-line fracture risk calculator called FRAX (accessible at https://www.sheffield.ac.uk/FRAX) is ≥3% for hip fracture or ≥20% for major osteoporosis-related fracture (hip, humerus, forearm and clinical vertebral fracture combined).[11]

Although estrogen (with or without a progestin) has been shown to improve bone mass and reduce fracture risk,[12,13] use of estrogen to reduce fracture risk has fallen out of favor for older women, but may be appropriate for younger postmenopausal women with vasomotor symptoms who also have low BMD.[14] Skeletal benefits of estrogen resolve quickly when treatment is stopped, but there does not seem to be a rebound increase in the risk for hip fractures or all fractures.[15] There are no data on risk of vertebral fractures after stopping estrogen.

Some of the medications shown to reduce fracture risk are shown in the Table 1. For simplicity, they are considered as either ''antiresorptive'' or ''anabolic'' (although these terms do not fully capture the issues). Most commonly used are the antiresorptives, four of which (alendronate, risedronate, zoledronic acid, and denosumab) have been shown to reduce the risk of spine, hip, and nonvertebral fractures. Although evidence for fracture reduction is equally strong for these four agents, long-term gains in BMD seem to be better with denosumab.[16] For most patients in a primary care setting, a low-cost generic oral bisphosphonate is often appropriate. Oral bisphosphonates must be taken on an empty stomach, with water only (but enough water to minimize the chance that the tablet will stick in the esophagus) with a 30 minute wait before taking anything else by mouth other than water. Zoledronic acid is given as an infusion once yearly and denosumab as a subcutaneous injection twice yearly. Raloxifene, a selective estrogen receptor modulator, has not been used as widely as these other agents because it has not been shown to reduce the risk of hip and other nonvertebral fractures; however, raloxifene is approved to reduce the risk of breast cancer and may be appropriate for women with osteoporosis with hip/spine discordance (BMD low in the spine, but not low in the hip).

The two drugs considered anabolics are teriparatide and abaloparatide. Both are given as daily subcutaneous injections for no longer than 2 years of treatment. Both have been shown to reduce the risk of vertebral and nonvertebral fractures, but the studies with these agents have been shorter duration and relatively small, compared with the antiresorptives, and specific hip fracture reduction has not been shown. Gains

Table 1. Medications Approved in the US for Treatment of Postmenopausal Osteoporosis

Drug	*Route, frequency*	*Evidence for fracture reduction*	*Duration*
Initial treatment for most patients			
Raloxifene	Oral, daily	Spine only	No limit
Alendronate	Oral, weekly	Spine, hip, nonvertebral	Consider a ''drug holiday'' after 5 years
Risedronate	Oral, weekly or monthly	Spine, hip, nonvertebral	
Zoledronic acid	IV, yearly	Spine, hip, nonvertebral	Consider a ''drug holiday'' after 3 years
Denosumab	SQ, twice yearly	Spine, hip, nonvertebral	No limit
Anabolic agents, usually reserved for most severely affected patients or those failing to respond to other drugs			
Teriparatide	SQ, daily	Spine, nonvertebral	Two-year limit; should be followed by agent from the list above
Abaloparatide	SQ, daily	Spine, nonvertebral	

IV, intravenous; SQ, subcutaneous.

in BMD appear greater and faster with abaloparatide, and fracture risk reduction with abaloparatide is at least as good as teriparatide and may be better.[17] These drugs are mostly used by specialists rather than primary care providers.

Treatment to reduce fracture risk is a long-term proposition. It is unlikely that medication for any chronic condition (*e.g.*, hypertension, hypercholesterolemia, and osteoporosis) can be stopped after a finite period with no further intervention needed. Thus, the anabolic agents mentioned above, although limited to 2 years of treatment, are usually followed by one of the antiresorptive agents.

Bisphosphonates accumulate in bone, so, after a period of ''loading,'' administration can be withheld for a ''drug holiday'' of at least 1 or 2 years. Limited data suggest that lower risk patients can start a ''holiday'' after 5 years of oral or 3 years of IV bisphosphonate, while higher risk patients should remain on oral treatment for 10 years or IV for at least 6 years.[18] The effects of denosumab are not sustained when treatment is stopped, so there is no ''drug holiday'' with denosumab,[19] but a 10-year study supports excellent long-term safety.[16]

Repeating DXA after 1–2 years of treatment and periodically after that is useful for monitoring treatment.[10] If bone density decreases or a fracture occurs, the patient should be reevaluated and treatment options reconsidered.

Before initiating pharmacologic treatment, laboratory studies should include calcium and creatinine (antiresorptive medication are contraindicated if hypocalcemia is present and bisphosphonates, either oral or IV, should not be given if kidney function is reduced—GFR should be above 30 or 35 mL/minutes). It is helpful to have a complete blood count, chemistry panel, serum phosphorus, and 25-OH D, which may uncover other health issues that need attention.[10]

Safety Concerns

Two rare safety issues have been associated with bisphosphonates and denosumab and have received widespread coverage in the lay press. Much of my time with patients involves lengthy discussions about osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF). ONJ was first reported in 2003 in cancer patients receiving doses of zoledronic acid $\sim 10\times$ higher than doses used to treat osteoporosis. In head-to-head trials in cancer patients, high-dose denosumab, $\sim 12\times$ higher than doses used to treat osteoporosis, was also found to be associated with ONJ, incidence for both zoledronic acid and denosumab is 1%–2% per year.[20] The incidence with lower doses and other drugs used to treat osteoporosis is thought to be around 1 in 10,000. ONJ can be extensive, painful, and disabling; however, most cases are localized, often painless, and respond to surgical removal of involved bone, antiseptic mouth rinse, and systemic antibiotics.[21] AFF involve the femoral shaft, occur with little or no trauma, are often preceded by weeks or months of prodromal groin or thigh pain and $\sim$30% are bilateral. They begin early as a lateral stress reaction with a lucent horizontal line and progress to become an oblique fracture with a medial spike.[22] (''Typical'' femur fractures, on the contrary, involve the hip, usually caused by the impact of a fall, affect only the side on which the patient landed, and have no warning symptoms). Surgical treatment of AFF involve placement of an intramedullary rod. Not only are AFF uncommon ($\sim$1–5 per 10,000 person years) but also mortality is much lower than that of the usual hip fracture.[23]

Recent reports are suggestive of a small but important increased risk of multiple vertebral fractures following discontinuation of denosumab.[24] Although it is tempting to consider stopping medication when a goal is reached, it is important to realize that none of our medications for chronic diseases has a prolonged durable effect. If the goal of treatment is to reduce fracture risk, some type of pharmacologic intervention is likely to be required life-long.

Shared Decision-Making

Patient understanding is important for acceptance of and persistence with treatment. Likely, this will require at least two visits with the physician and healthcare team—one visit to start the process with a FRAX and, if appropriate, order for DXA measurement, and a second visit to discuss the results and develop a management plan that is acceptable to the patient. Sample patient information material is available from the American Association of Clinical Endocrinologists (https://www.empoweryourhealth.org/sites/all/files/AACE_Osteoporosis_Decision_Aid_B.pdf) and may be helpful to provide to patients.

Guidelines

Useful guidelines are available from the National Osteoporosis Foundation[8] and the American Association of Clinical Endocrinologists.[10] These and earlier guidelines share a great deal of agreement and consistency. Recently, the American College of Physicians has issued guidelines[25] that ways are at odds with those from other groups and counter-intuitive, including a treatment duration of only 5 years (weak recommendation; low-quality evidence) and a recommendation against bone density testing during the 5-year treatment period (weak recommendation; low-quality evidence).

Persistence with Treatment

For diseases in which patients are asymptomatic, persistence with treatment to reduce risk of future adverse events is poor. With some treatments for osteoporosis, publicity about rare but concerning safety issues (ONJ, AFF) has contributed to lack of acceptance or continuation of treatments. Understanding patients' decision-making[26] and providing accurate information—that in most cases, benefits of treatment far outweigh the risks—are essential for optimal long-term management of this potentially serious disorder.[27]

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Author Disclosure Statement

N.B.W. serves on speaker bureaus for Amgen and Radius and advisory boards for Amgen and Radius.

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