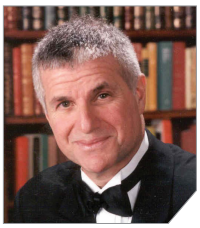
UPDATE Bone health



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In this Update: BMD testing—understanding who to scan and what sites to evaluate, ospemifene's effects on bone, assessing for sarcopenia as well as osteoporosis, and aromatase inhibitors and treatment for fracture prevention

Prior to last year, this column was titled "Update on osteoporosis." My observation, however, is that too many ObGyn providers simply measure bone mass (known as bone mineral density, or BMD), label a patient as normal, osteopenic, or osteoporotic, and then consider pharmacotherapy. The FRAX fracture prediction algorithm, which incorporates age, weight, height, history of any previous fracture, family history of hip fracture, current smoking, use of glucocorticoid medications, and any history of rheumatoid arthritis, has refined the screening process somewhat, if and when it is utilized. As clinicians, we should never lose sight of our goal: to prevent fragility fractures. Having osteoporosis increases that risk, but not having osteoporosis does not eliminate it.

In this Update, I highlight various ways in which work published this past year may help us to improve our patients' bone health and reduce fragility fractures.

IN THIS ARTICLE

Updated ISCD guidance emphasizes appropriate BMD testing, use of the Z-score, and terminology

International Society for Clinical Densitometry. 2019 ISCD Official Positions–Adult. June 2019. https://www.iscd.org/official-positions/2019-ISCD-official-positions-adult.

In 2019, the International Society for Clinical Densitometry (ISCD) updated all its official positions from 2015.[1] I will summarize the points that are important for ObGyn providers. We are and should be, I believe, the first-line protectors of women's bone health.

Indications for BMD testing

The ISCD's indications for BMD testing remain for women age 65 and older. For postmenopausal women younger than age 65, a BMD test is indicated if they have a risk factor for low bone mass, such as 1) low body weight, 2) prior fracture, 3) high-risk medication use, or 4) a disease or condition associated with bone loss. A BMD test also is indicated for women during the menopausal transition with clinical risk factors for fracture, such as

low body weight, prior fracture, or high-risk medication use. Interestingly, the ISCD recommendation for men is similar but uses age 70 for this group.

In addition, the ISCD recommends BMD testing in adults with a fragility fracture, with a disease or condition associated with low bone mass, or taking medications associated with low bone mass, as well as for anyone being considered for pharmacologic therapy, being treated (to monitor treatment effect), not receiving therapy in whom evidence of bone loss would lead to treatment, and in women discontinuing estrogen who should be considered for BMD testing according to the indications already mentioned.

Sites to assess for osteoporosis. The World Health Organization international reference standard for osteoporosis diagnosis is a T-score of -2.5 or less at the femoral neck. The reference standard, from which the T-score is calculated, is for white women aged 20 to 29 years of age from the database of the Third National Health and Nutrition Examination Survey. Osteoporosis also may be diagnosed in postmenopausal women if the T-score of the lumbar spine, total hip, or femoral neck is -2.5 or less. In certain circumstances, the 33% radius (also called the one-third radius) may be utilized. Other hip regions of interest, including Ward's area and the greater trochanter, should *not* be used for diagnosis.

The skeletal sites at which to measure BMD include the anteroposterior of the spine and hip in all patients. In terms of the spine, use L1–L4 for spine BMD measurement. However, exclude vertebrae that are affected by local structural changes or artifact. Use 3 vertebrae if 4 cannot be used, and 2 if 3 cannot be used. BMD-based diagnostic classification should not be made using a single vertebra. Anatomically abnormal vertebrae may be excluded from analysis if they are clearly abnormal and nonassessable within the resolution of the system, or if there is more than a 1.0 T-score difference between the vertebra in question and adjacent vertebrae. When vertebrae are excluded, the BMD of the remaining vertebrae are used to derive the T-score.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Patients commonly ask for BMD testing and ObGyn providers commonly order it. Understanding appropriate use of BMD testing in terms of who to scan, what sites to evaluate, when there may be spurious results of vertebrae due to artifacts, avoiding T-scores in premenopausal women in favor of Z-scores, understanding that *low bone mass* is a preferred term to *osteopenia,* and knowing how to order and use serial BMD testing will likely improve our role as the frontline providers to improving bone health in our patients.

For BMD measurement at the hip, the femoral neck or total proximal femur—whichever is lowest—should be used. Either hip may be measured. Data are insufficient on whether mean T-scores for bilateral hip BMD should be used for diagnosis.

Terminology. While the ISCD retains the term *osteopenia*, the term *low bone mass* or *low bone density* is preferred. People with low bone mass or density are not necessarily at high fracture risk.

Concerning BMD reporting in women prior to menopause, Z-scores, not T-scores, are preferred. A Z-score of -2.0 or lower is defined as "below the expected range for age"; a Z-score above -2.0 is "within the expected range for age."

Use of serial BMD testing

Finally, regarding serial BMD measurements, such testing in combination with clinical assessment of fracture risk can be used to determine whether treatment should be initiated in untreated patients. Furthermore, serial BMD testing can monitor a patient's response to therapy by finding an increase or stability of bone density. It should be used to monitor individuals following cessation of osteoporosis drug therapy. Serial BMD testing can detect loss of bone density, indicating the need to assess treatment adherence, evaluate possible secondary causes of osteoporosis, and possibly re-evaluate therapeutic options.

Intervals between BMD testing should be determined according to each patient's clinical status. Typically, 1 year after initiating or changing therapy is appropriate, with longer intervals once therapeutic effect is established.

FAST TRACK

The ISCD recommends BMD testing in adults with a fragility fracture, with a condition associated with low bone mass, or taking medications associated with low bone mass

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Dyspareunia drug has positive effects on bone

de Villiers TJ, Altomare C, Particco M, et al. Effects of ospemifene on bone in postmenopausal women. Climacteric. 2019;22:442-447.

Ospemifene is a selective estrogen receptor modulator (SERM), given daily and orally, that was approved by the US Food and Drug Administration (FDA) in 2013 for moderate to severe dyspareunia due to menopause-related vulvovaginal atrophy (VVA). More recently, the indication has been extended to include vaginal dryness of menopause. Other SERMs have shown efficacy in prevention and treatment of osteoporosis, including raloxifene, which was FDA approved for the respective indications in 1997 and 1999, and lasofoxifene, which showed efficacy but was not approved in the United States.[2]

Previously, ospemifene effectively reduced bone loss in ovariectomized rats, with activity comparable to that of estradiol and raloxifene.[3] Clinical data from 3 phase 1 or 2 clinical trials found that ospemifene 60 mg/day had a positive effect on biochemical markers for bone turnover in healthy postmenopausal women, with significant improvements relative to placebo and effects comparable to those of raloxifene.[4]

Effects on bone formation/resorption biomarkers

In a recent study, de Villiers and colleagues reported the first phase 3 trial that looked at markers of bone formation and bone resorption.[5] A total of 316 women were randomly assigned to receive ospemifene, and 315 received placebo.

Demographic and baseline characteristics were similar between treatment groups. Participants' mean age was approximately 60 years, mean body mass index (BMI) was 27.2 kg/m^2, and mean duration of VVA was 8 to 9 years. Serum levels of 9 bone biomarkers were similar between groups at baseline.

At week 12, all 5 markers of bone resorption improved with ospemifene treatment, and 3 of the 5 (NTX, CTX, and TRACP-5b) did so in a statistically significant fashion compared with placebo ($P \leq .02$). In addition, at week 12, all 4 markers of bone formation improved with ospemifene treatment compared with placebo ($P \leq .008$). Furthermore, lower bone resorption markers with ospemifene were observed regardless of time since menopause (≤ 5 years or > 5 years) or baseline BMD, whether normal, osteopenic, or osteoporotic.

Interpret results cautiously

The authors caution that the data are limited to biochemical markers rather than fracture or BMD. It is known that there is good correlation between biochemical markers for bone turnover and the occurrence of fracture.[6]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Ospemifene is an oral SERM approved for the treatment of moderate to severe dyspareunia as well as dryness from VVA due to menopause. The preclinical animal data and human markers of bone turnover all support the antiresorptive action of ospemifene on bones. Thus, one may safely surmise that ospemifene's direction of activity in bone is virtually indisputable. The magnitude of that activity is, however, unstudied. Therefore, when choosing an agent to treat women with dyspareunia or vaginal dryness from VVA of menopause, determining any potential add-on benefit in bone may be appropriate for that particular patient, although one would not use it as a stand-alone agent for bone only.

Sarcopenia adds to osteoporotic risk for fractures

Lima RM, de Oliveira RJ, Raposo R, et al. Stages of sarcopenia, bone mineral density, and the prevalence of osteoporosis in older women. Arch Osteoporos. 2019;14:38.

Osteoporotic fractures impose a significant burden on health care costs and increase the risk for disability and mortality, especially as life expectancy increases.[7]

In 1989, the term *sarcopenia* was introduced to refer to the age-related decline in skeletal muscle mass.[8] Currently, sarcopenia is defined as a progressive decline in muscle mass, strength, and physical function, thus increasing the risk for various adverse outcomes, including osteoporosis.[9] Although muscle and bone tissues differ morphologically, their functioning is closely interconnected.

The sarcopenia-osteoporosis connection

Lima and colleagues sought to investigate the relationship between sarcopenia and osteoporosis.[10] They measured women's fat free mass with dual-energy x-ray absorptiometry (DXA) scanning, muscle strength using a dynamometer to measure knee extension torque while participants were seated, and functional performance using the timed "up and go test" in which participants were timed as they got up from a chair, walked 3 meters around a cone, and returned to sit in the chair.[10,11]

The authors used definitions from the European Working Group on Sarcopenia in Older People (EWGSOP). Participants who had normal results in all 3 domains were considered nonsarcopenic. Presarcopenia was defined as having low fat free mass on DXA scanning but normal strength and function. Participants who had low fat free mass and either low strength or low function were labeled as having sarcopenia. Severe sarcopenia was defined as abnormal results in all 3 domains.

Two hundred thirty-four women (mean age, 68.3 years; range, 60–80) underwent BMD testing and were evaluated according to the 3 domains of possible sarcopenia. All were community dwelling and did not have cognitive impairment or functional dependency.

The rates of osteoporosis were 15.8%, 19.2%, 35.3%, and 46.2% for nonsarcopenia, presarcopenia, sarcopenia, and severe sarcopenia, respectively ($P=.002$). Whole-body and femoral neck BMD values were significantly lower among all sarcopenia stages when compared with nonsarcopenia ($P<.05$). The severe sarcopenia group showed the lowest lumbar spine T-scores ($P<.05$). When clustered, sarcopenia and severe sarcopenia presented a significantly higher risk for osteoporosis (odds ratio, 3.4; 95% confidence interval [CI], 1.5–7.8).

Consider sarcopenia a risk factor

The authors concluded that these "results provide support for the concept that a dose-response relationship exists between sarcopenia stages, BMD, and the presence of osteoporosis. These findings strengthen the clinical significance of the EWGSOP sarcopenia definitions and indicate that severe sarcopenia should be viewed with attention by healthcare professionals."

FAST TRACK

When clustered, sarcopenia and severe sarcopenia presented a significantly higher risk for osteoporosis (OR, 3.4; 95% CI, 1.5–7.8)

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Osteoporotic fractures are defined as fragility fractures. While "frailty" has been a risk factor for such fractures in the past, increasing evidence now suggests that what we previously called frailty includes a significant component of loss of muscle mass, strength, and function—referred to as sarcopenia. While it is not likely that many ObGyns will perform objective testing for sarcopenia, conducting even a subjective assessment of such status should be considered in addition to BMD determinations in making decisions about pharmacotherapy.

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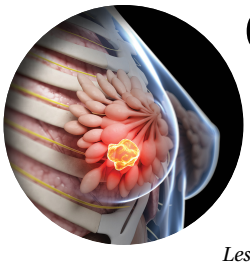

Certain characteristics may offset fracture risk in aromatase inhibitor users

Leslie WD, Morin SN, Lix LM, et al. Fracture risk in women with breast cancer initiating aromatase inhibitor therapy: a registry-based cohort study. Oncologist. 2019;24:1432-1438.

FAST TRACK

After adjusting for all covariates, AI users were not at significantly greater risk for major osteoporotic fractures, hip fracture, or any fracture compared with the general population

As ObGyn providers, we often treat women who have been diagnosed and treated for breast cancer. Initially, tamoxifen was the mainstay of hormonal adjuvant therapy. More recently, aromatase inhibitors (AIs) have played an increasing role in the treatment of women with estrogen receptor–positive breast cancer.[12]

The use of AIs increases bone turnover and induces bone loss at trabecular-rich bone sites at an average rate of 1% to 3% per year, with reports of up to a threefold increased fracture incidence.[13] By contrast, a large nationwide population-based cohort study using US Medicare data identified minimal fracture risk from AI use compared with tamoxifen use (11% higher for nonvertebral fractures, not significantly increased for hip fractures).[14]

An article published previously in this column reported that women on AIs treated with intravenous zoledronic acid had improvements in BMD, while women treated with denosumab had statistically significant fewer fractures compared with those receiving placebo, whether they had normal bone mass, osteopenia, or osteoporosis at baseline.[15-17]

Data derived from a population-based BMD registry

In a recent cohort study, Leslie and colleagues offer the opinion that "observations in the clinical trial setting may differ from routine clinical practice."[18] The authors examined fracture outcomes using a large clinical registry of BMD results from women in Manitoba, Canada. They identified women at least 40 years of age initiating AI therapy for breast cancer (n = 1,775), women with breast cancer not receiving AI therapy (n = 1,016), and women from the general population without breast cancer (n = 34,205).

Fracture outcomes were assessed after a mean of 6.2 years for the AI users, all of whom had at least 12 months of AI exposure. At baseline, AI users had higher BMI, higher BMD, lower osteoporosis prevalence, and fewer prior fractures than women from the general population or women with breast cancer without AI use (all $P<.001$). After adjusting for all covariates, AI users were not at significantly greater risk for major osteoporotic fractures (hazard ratio [HR], 1.15; 95% CI, 0.93–1.42), hip fracture (HR, 0.90; 95% CI, 0.56–1.43), or any fracture (HR, 1.06; 95% CI, 0.88–1.28) compared with the general population.

Results challenge prevailing view

Thus, the authors concluded that higher baseline BMI, BMD, and lower prevalence of prior fracture at baseline may offset the adverse effects of AI exposure. Although confirmatory data from large cohort studies are required, the authors stated that their findings challenge the view that all women with breast cancer initiating AI therapy should be considered at high risk for fracture. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

It is well known that women with estrogen receptor–positive breast cancers tend to be more obese than noncancer patients and have higher levels of circulating estrogens. The study by Leslie and colleagues shows that such patients will have fewer previous fractures and better baseline bone mass values than the general population. This may prompt us to rethink whether *all* women initiating AI therapy need to be treated for fracture prevention, as some previous studies have suggested. Clearly, further study is necessary.

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