



# OSTEOPOROSIS

A look at recent expert guidelines and key studies in bone health, the findings of which affect your patients young and old



**>> Steven R. Goldstein, MD**

Dr. Goldstein is Professor of Obstetrics and Gynecology at New York University School of Medicine in New York City. He is Director of Gynecologic Ultrasound and Co-Director of Bone Densitometry at New York University Medical Center in New York City. Dr. Goldstein serves on the OBG MANAGEMENT Board of Editors.

*The author reports that he is a speaker for Warner Chilcott and Shionogi.*

**B**ecause the low bone mass and deterioration of bone microarchitecture and quality that characterize osteoporosis can lead to fragility fracture, it is vital that we intervene in our patients' health in a timely manner to reduce this risk. One way to accomplish this goal is to understand the role of age in determining a woman's fracture risk. For example, an 80-year-old woman and a 50-year-old woman with a T-score of -2.5, as measured by dual x-ray absorptiometry (DXA), will have dramatically different fracture risks. According to the World Health Organization's fracture-risk assessment tool (<http://www.shef.ac.uk/FRAX/>), the older woman has a 10-year probability of hip fracture approximately five times greater than the younger woman.

Although no new therapies have been approved during the past year, several important findings were published that affect

clinical management of menopausal patients or suggest changes likely in the future.

In this article, I review:

- the latest guidance on osteoporosis from the American College of Obstetricians and Gynecologists (ACOG)
- the most recent indications for bone mineral density (BMD) testing from the International Society for Clinical Densitometry (ISCD)
- a study exploring the effect of oral hormonal contraception on the acquisition of peak BMD in adolescents and young women
- results of a randomized trial of the experimental agent odanacatib in postmenopausal women
- a pilot study of teriparatide (Forteo) for idiopathic osteoporosis in premenopausal women.

## ACOG issues recommendations on screening, treatment, and lifestyle

*Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin #129: Osteoporosis. Obstet Gynecol. 2012;120(3):718–734.*

**T**his comprehensive review of management guidelines for ObGyns deserves “top billing” in this update. It offers recommendations on important interventions, from BMD

### IN THIS ARTICLE

#### Indications for BMD assessment

page 36

#### How “the pill” affects bone accrual in adolescents and young women

page 38

#### One management option for idiopathic osteoporosis in premenopausal women

page 40

### ON THE WEB

**Dr. Goldstein discusses the best OC dose, keeping bone health in mind, for your young adult and adolescent patients, at [obgmanagement.com](http://obgmanagement.com)**



**WHAT THIS EVIDENCE MEANS FOR PRACTICE**

By utilizing the FRAX risk-assessment tool, we can determine which patients truly require treatment. In the process, we should be able to reduce the overtreatment of younger women with low bone mass as well as the undertreatment of older women who appear to have less deranged bone mass.

ACOG also emphasizes the need to avoid the overutilization of DXA scans in various groups, as well as the importance of lifestyle adjustments to promote bone health in all age groups.

measurement and subsequent monitoring to calcium and vitamin D supplementation.

**When to initiate screening**

- Begin BMD screening using DXA at age 65. DXA also may be appropriate for younger women if they are postmenopausal and have other significant risk factors for osteoporosis or fracture (**Level A evidence** – based on good and consistent scientific evidence).
- In the absence of new risk factors, do not perform DXA screening more frequently than every 2 years (**Level B evidence** – based on limited or inconsistent scientific evidence).

**Which patients should be treated?**

- Treatment is recommended for:
  - women with a T-score of -2.5 or lower
  - women who have had a low-trauma fracture
  - women with a T-score between -1 and -2.5 and a 10-year FRAX hip-fracture risk of 3% or higher or a 10-year FRAX risk

of major osteoporotic fracture of 20% or higher, or both. A major osteoporotic fracture involves the forearm, hip, or shoulder, or a clinical vertebral fracture (**Level A evidence**).

- Only therapies approved by the US FDA should be used for medical treatment. They are raloxifene (Evista), bisphosphonates (Actonel, Boniva, Fosamax, Reclast), parathyroid hormone, denosumab (Prolia), and calcitonin (Fortical, Miacalcin) (**Level A evidence**).

**Monitoring of therapy**

In the absence of new risk factors, do not repeat DXA monitoring of therapy once BMD has been determined to be stable or improved (**Level B evidence**).

**Lifestyle recommendations**

- Counsel women about lifestyle factors that may affect BMD and fracture risk, which include smoking, poor nutrition and excessive weight loss, weight-bearing and muscle-strengthening exercise, and fall prevention (**Level B evidence**).
- Advise patients of current recommendations for calcium and vitamin D intake from the Institute of Medicine, which are calcium 1,200 mg/day and vitamin D 600 IU/day for women aged 51 to 70 years (**Level B evidence**).
- Counsel girls and women of all ages about the effects of lifestyle on bone health (**Level C evidence** – based on consensus and expert opinion).



The FRAX risk-assessment tool can aid in determining which patients truly require treatment for low bone mass

## Clinical densitometrists weigh in on indications for BMD assessment

*International Society for Clinical Densitometry (ISCD). Indications for bone mineral density (BMD) testing. <http://www.iscd.org/official-positions/2013-iscd-official-positions-adult/>. Updated August 15, 2013. Accessed November 7, 2013.*

In its comprehensive review of BMD assessment, the ISCD elucidates the process, which typically involves DXA imaging.

**Indications for BMD assessment**

- The female patient is age 65 or older

- The postmenopausal patient is younger than age 65 but has a risk factor for low bone mass, such as low body weight, a history of fracture, use of a high-risk medication, or a disease or condition associated with bone loss
- The perimenopausal woman has clinical risk factors for fracture, such as low body weight, history of fracture, or use of a high-risk medication
- The adult sustains a fragility fracture
- The adult has a disease or condition associated with low bone mass or bone loss
- The adult is taking a medication associated with low bone mass or bone loss
- The patient is being considered for pharmacologic therapy
- The patient is being treated, to monitor effect
- The patient is not receiving therapy, but evidence of bone loss would lead to treatment.

#### When serial BMD assessment is appropriate

- When it is used to determine whether treatment should be initiated (in untreated patients) because of significant bone loss
- To monitor response to therapy by identifying an increase or stabilization of BMD
- To identify nonresponse by documenting a loss of BMD, suggesting the need for treatment re-evaluation and assessment for a secondary cause of osteoporosis
- To follow-up earlier assessment when the expected change in BMD equals or exceeds the least significant change
- When the interval is appropriate for the patient's clinical status. (In general, BMD assessment is performed 1 year after initiation or change of therapy, with longer intervals once a therapeutic effect has been established.)
- When the patient is using a medication associated with rapid bone loss, such as glucocorticoid therapy. In such a patient, more frequent testing may be appropriate. Note that these recommendations differ slightly from ACOG's statements regarding the use of DXA.

#### Diagnosis of osteoporosis

- According to the WHO international reference standard, osteoporosis can be diagnosed when a patient has a T-score of  $-2.5$  or below at the femoral neck. The reference standard from which the T-score is calculated is the white female population aged 20 to 29 years in the National Health and Nutrition Examination Survey (NHANES) III database.
- Osteoporosis also may be diagnosed in postmenopausal women and men aged 50 or older when the T-score of the lumbar spine, total hip, or femoral neck is  $-2.5$  or below. In some circumstances, the 33% radius (also called the 1/3 radius) may be utilized.
- Other hip regions of interest, including Ward's area and the greater trochanter, should not be used for diagnosis.

#### A move away from use of the term "osteopenia"

- The term may be retained, but "low bone mass" or "low bone density" is preferred
- People with low bone mass or low bone density do not necessarily have a high risk of fracture.

#### WHAT THIS EVIDENCE MEANS FOR PRACTICE

DXA testing remains the cornerstone of diagnosis for patients at risk for fragility fracture. It also is the optimal method to determine the need for pharmacotherapy. In some instances, however, overutilization of DXA imaging has led to overtreatment, especially in younger women with low bone mass, when treatment is based on variables other than diminished bone quality (including, "small-boned" women, genetics, and failure to achieve peak bone mass as high as one's peer group prior to menopause).

These recommendations help to clarify the rationale for follow-up DXA imaging for patients on therapy, an area in which scientific unanimity is lacking.



**According to the World Health Organization, osteoporosis can be diagnosed when a patient has a T-score of  $-2.5$  or below at the femoral neck**

CONTINUED ON PAGE 38



# In adolescents and young women, consider the bone effects of oral contraceptives

Ziglar S, Hunter TS. *The effect of hormonal oral contraception on acquisition of peak bone mineral density of adolescents and young women. J Pharm Pract. 2012;25(3):331-340.*

The bone loss observed in adolescents and young women who use depot medroxyprogesterone acetate (Depo-Provera) for contraception led to an FDA-mandated boxed warning on the medication's package insert. The effect of oral contraceptives (OCs) on bone growth has received little publicity, however.

The best strategy to offset the natural loss of bone associated with aging and the menopausal transition is to ensure the development of maximal bone mass in youth. When maximal BMD is not achieved, the risk of osteoporosis is increased.

Adolescence is a critical period of bone mineralization, which is mediated by endogenous estradiol. The highest rate of bone mass accrual occurs 1 year before and 3 years after menarche. Young women who consume a diet low in calcium or who have an eating disorder, who fail to exercise, who smoke, or who have low estrogen status are most likely to have low peak bone mass.

OCs suppress endogenous estradiol production by interrupting the hypothalamic-pituitary-ovarian axis. By replacing endogenous estradiol with ethinyl estradiol (EE), OCs establish and maintain new hormone levels. Early initiation and use of very-low-dose EE increases the likelihood that the accrual of bone mass will be jeopardized at a critical time of bone mineralization.

### Details of this meta-analysis

Ziglar and Hunter reviewed 11 prospective trials that showed a decrease in bone mass in adolescents and young women who used low-dose OCs, six trials that showed a neutral effect, and one trial that found an increase in bone mass. This last study involved only members of the US military whose level of daily exercise may not be representative of the general population of women the same age. Investigators also theorized that the use of norethindrone acetate as an androgenic progestin in this study may have exerted a positive effect on bone accrual.

Ziglar and Hunter concluded that the use of OCs containing 20 µg EE prevents adolescents and young women from attaining peak BMD. Evidence on the effect of contraceptives formulated with 30 to 35 µg EE is less definitive, but this dose may also impede BMD acquisition in adolescents.

### FAST TRACK

Because it may limit the accrual of bone mass, the lowest-dose oral contraceptive may not be the best clinical choice for adolescents and young women seeking contraception

### ON THE WEB

Dr. Goldstein discusses the best OC dose, keeping bone health in mind, for your young adult and adolescent patients, at [obgmanagement.com](http://obgmanagement.com)

### WHAT THIS EVIDENCE MEANS FOR PRACTICE

To ensure breast health and reduce the risk of venous thromboembolic events, drug makers have developed OCs with lower and lower doses of EE. In the process, however, the beneficial effects of endogenous estradiol on bone acquisition have been suppressed. Therefore, the lowest-dose OC may not necessarily be the most appropriate clinical choice for adolescents and young women seeking contraception.

# Experimental drug reduces bone resorption without impeding bone formation

*Brixen K, Chapurlat R, Cheung AM, et al. Bone density, turnover, and estimated strength in postmenopausal women treated with odanacatib: a randomized trial. J Clin Endocrinol Metab. 2013;98(2):571-580.*

Current treatments for osteoporosis include antiresorptive agents, such as bisphosphonates and denosumab, that preserve bone mass by reducing the rate of bone turnover. These drugs reduce the number or activity (or both) of bone-resorbing osteoclasts. Because osteoclasts play a role in stimulating bone formation by osteoblasts, these treatments indirectly lower bone formation.

Odanacatib is a drug in Phase 3 development for the treatment of postmenopausal osteoporosis. It is a highly selective and reversible oral inhibitor of the collagenase activity of cathepsin K, which is secreted by osteoclasts. Odanacatib reduces bone resorption without reducing the number of osteoclasts and, thus, appears to preserve bone formation.

## Details of the trial

Brixen and colleagues conducted a randomized, double-blind, international, 2-year, Phase 3 trial comparing odanacatib 50 mg once weekly with placebo in postmenopausal women treated with calcium and vitamin D. The primary endpoint was the change from baseline BMD at the lumbar spine at 1 year, as assessed by DXA. Secondary endpoints included the change from baseline BMD at

the hip (total hip, femoral neck, and trochanter) at 1 year, the change from baseline BMD at the spine and hip at 2 years, and 1- and 2-year changes in bone-turnover markers. A total of 214 women were enrolled (average age: 64 years; average T-score of 1.8 at the lumbar spine, -1.8 at the femoral neck, and -1.3 at the total hip).

At 1 year, the change from baseline BMD at the lumbar spine was significantly higher ( $P < .001$ ) in women receiving odanacatib, compared with placebo (treatment difference: 3.5%). At 2 years, the treatment difference was even higher (5.4%). The mean changes in BMD at the femoral neck, total hip, and trochanter also were significantly greater ( $P < .001$ ) in women receiving odanacatib, with treatment differences at 2 years of 3.8%, 3.3%, and 5.5%, respectively.

During the first 6 months of the trial, serum concentrations of bone-turnover markers (CTX and P1NP) decreased significantly ( $P < .001$ ) in odanacatib-treated women, compared with those given placebo.

## WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although no new agents for the treatment of osteoporosis have been introduced over the past year, cathepsin K inhibitors appear to offer great promise for the future. As clinicians, we need to keep abreast of new developments that may be of potential value to our patients.



**Because the experimental agent odanacatib reduces bone resorption without reducing the number of osteoclasts, it may preserve bone formation**

CONTINUED ON PAGE 40



# Pilot study: Teriparatide was effective in 81% of premenopausal women with idiopathic osteoporosis

*Cohen A, Stein EM, Recker RR, et al. Teriparatide for idiopathic osteoporosis in premenopausal women: A pilot study. J Clin Endocrinol Metab. 2013;98(5):1971-1981.*

**I**diopathic osteoporosis (IOP) affects young, otherwise healthy men and women with intact gonadal function and no secondary cause of bone loss or fragility. Women with IOP have abnormal bone microarchitecture with thinner cortices; fewer, thinner, and more widely separated and heterogeneously distributed trabeculae; more rod-like trabecular structures; less trabecular stiffness; and a higher level of marrow fat.

The osteoanabolic agent teriparatide increases BMD and reduces the incidence of fracture in postmenopausal women and in patients with glucocorticoid-induced osteoporosis, and it increases BMD in men with IOP. This study explored its effect in premenopausal women with IOP.

## Details of the study

Cohen and colleagues recruited premenopausal women aged 20 to 48 years who had one or both of the following traits:

- a history of at least one low-trauma fracture more than 6 months before enrollment
- low BMD of the spine or hip (Z-score of -2.0 or below), as assessed by DXA.

All participants had regular menses and early follicular-phase follicle-stimulating hormone (FSH) levels below 20 mIU/mL; none were using hormonal contraception. Women who had secondary osteoporosis related to estrogen deficiency, an eating disorder, an endocrinopathy, celiac or gastrointestinal disease,

hyperparathyroidism, marked hypercalcaemia, a low serum level of 25-hydroxyvitamin D (<20 ng/mL), and drug exposures were excluded.

All participants (n = 21) received teriparatide 20 µg daily in the morning or evening, according to preference. They also were given calcium 630 mg and vitamin D 800 IU daily.

BMD increased at the spine by 10.8% (standard deviation: 8.3%), total hip by 6.2% (5.6%), and femoral neck by 7.6% (3.4%) (all *P* <.001). Transiliac biopsies demonstrated significant increases in cortical width and porosity, and trabecular bone volume and number increased as well. Four women had no increase in BMD.

Overall, Cohen and colleagues concluded that teriparatide was associated with increased BMD at the spine and hip and improved trabecular microarchitecture and stiffness at the iliac crest in the majority of women with IOP.



**Teriparatide appears to be an excellent agent for the majority of premenopausal patients with idiopathic osteoporosis**

## WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although ObGyns rarely prescribe teriparatide, often leaving this option for metabolic bone experts to offer, we should keep premenopausal IOP in mind when younger patients sustain low-trauma fractures of the hip or vertebrae, as well as fracture of an upper or lower extremity or the ribs.

Teriparatide appears to be an excellent choice for the majority of premenopausal patients with IOP (81% of patients in this pilot study).