OSTEOPOROSIS

What we've learned about when to measure BMD and how to identify lesser-known causes of bone loss, as well as the value of quantitative ultrasound in determining the risk of fracture. And in the pipeline: a drug that curbs bone resorption without limiting bone formation.

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Osteoporosis is a significant health issue—and it is likely to remain so as more and more women live longer and longer. In fact, increasing age is the single biggest risk factor for osteoporotic fragility fracture.

Over the past year, important research has improved our understanding in diverse areas of bone health. In this Update, I highlight studies that:

- seek to elucidate the optimal frequency of dual-energy x-ray absorptiometry (DXA) imaging to assess bone mineral density
- review secondary causes of osteoporosis besides menopause-related estrogen deficiency
- explore the use of quantitative ultrasound (QUS) to predict the risk of fracture
- report on a new class of pharmaceutical agents that inhibit the bone-resorption enzyme Cathepsin K.

All of these issues are clinically relevant to the ObGyn specialty because, when it comes to our patients' bone health, we often function as the primary care physician.

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Two trials of quantitative ultrasound to predict the risk of fracture
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ON THE WEB

Dr. Goldstein describes an evidence-based approach to BMD assessment, at obgmanagement.com

When is DXA indicated—and how often should it be repeated?

Gourlay ML, Fine JP, Preisser JS, et al; Study of Osteoporotic Fractures Research Group. Bone-density testing interval and transition to osteoporosis in older women. N Engl J Med. 2012;366(3):225–233.

Lewiecki EM, Laster AJ, Miller PD, Bilezikian JP. More bone density testing is needed, not less. J Bone Miner Res. 2012;27(4):739–742.

American Society for Bone and Mineral Research response to media coverage of New England Journal of Medicine *study: "Bone density testing interval and transition to osteoporosis in older women" [press release]. http://www.asbmr.org/about/pressreleases/detail.aspx?cid=3801baff-0df3-47c0-874f-08a185d67001. Published February 1, 2012. Accessed October 15, 2012.*

Recommendations from professional societies, such as the National Osteoporosis

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Foundation, the International Society of Clinical Densitometry, and the American College of Obstetricians and Gynecologists say virtually the same thing about DXA imaging: **Screening is appropriate for women 65 years and older and for postmenopausal women younger than age 65 who have risk factors for fracture.** Risk factors include:

- history of a fragility fracture
- body weight less than 127 lb
- medical causes of bone loss, such as medication or disease
- parental history of hip fracture
- current smoker
- alcoholism
- rheumatoid arthritis.

The measurement of bone mineral density (BMD) has been the cornerstone of the diagnosis of osteopenia and osteoporosis since these classifications were introduced by the World Health Organization (WHO) in 1994. Although we are now able to evaluate a woman's fracture risk using the FRAX tool, which does not require BMD assessment, DXA scanning has become entrenched in routine clinical practice in the United States. In addition, patients who use drugs to reduce their fracture risk often demand periodic testing to see how they are doing. Even women who do not take medications often want periodic assessment to confirm that they are not "losing bone." Medicare allows for testing every 23 months.

23-month screening interval does not fit all women

Gourlay and colleagues prospectively followed 4,957 women aged 67 years or older who had no history of hip or vertebral fracture and who were not being treated for osteoporosis. After follow-up for as long as 15 years, investigators found that the better a woman's initial bone density, the longer it took for her to develop osteoporosis. For example, among women over 67 years of age who had a T-score of –1.0 or better, it would take 16.8 years for 10% of this population to develop osteoporosis. In contrast, among women over 67 years of age who had a T-score of –2.0, it would take only 1.1 years for 10% of this population to develop osteoporosis.

This finding certainly calls into question the notion that all patients should be screened every 23 months. It may be better to think of screening as a way of triaging patients for decisions relative to subsequent follow-up.

Media distorted take-home message

This study was the focus of considerable attention from the media, which implied that too much DXA screening is being performed. In reality, only 13% of women over the age of 65 undergo a baseline DXA scan. However, routine follow-up of all patients at 23-month intervals is clearly not appropriate.

Because this study primarily involved white women older than age 67, extrapolation of its findings to other groups may not be appropriate. Nevertheless, the study helps to underscore the fact that reliance on BMD measurement alone should not be used to determine the need for therapeutic intervention. The FRAX tool can be used on an annual basis to assess a woman's risk of fracture and does not require follow-up DXA imaging at any arbitrary interval.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

In healthy older women, an interval of 23 months for repeat BMD assessment makes little sense. For women who have excellent initial T-scores, clinicians can lengthen this interval significantly.

However, strict reliance on the T-score isn't the best way to predict a woman's fracture risk or determine when pharmacologic intervention is warranted. Rather, yearly assessment using a tool such as FRAX should become the standard of care.

FAST TRACK

Only 13% of women over the age of 65 undergo a baseline DXA scan

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Some secondary causes of osteoporosis are overlooked or underappreciated

Miller PD. Unrecognized and unappreciated secondary causes of osteoporosis. Endocrinol Metab Clin North Am. 2012;41(3):613–628.

FAST TRACK

Among the drugs that can cause bone loss in our patients are aromatase inhibitors, DMPA, proton pump inhibitors, and GnRH agonists

The fractures traditionally associated with osteoporosis involve the hip and vertebrae, although low-trauma fractures of the humerus, forearm, femur shaft, tibia, and fibula are also associated with a high risk of future fracture in untreated women.

Once a clinician is confident that a patient has osteoporosis, the question is whether the diagnosis is postmenopausal osteoporosis—or some other form of the disease. Although estrogen deficiency is the most common cause of osteoporosis in postmenopausal women, many other conditions may accompany estrogen deficiency and contribute to impaired bone strength in this population.

Among the culprits are some conditions that are not often encountered in the average gynecologic practice: monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, celiac disease, Crohn's disease, and other inflammatory bowel diseases. In addition, bariatric surgery, eating disorders, primary hyperparathyroidism, and a number of medications have been implicated in BMD loss or increased risk of fracture, or both. Among the problematic drugs of particular interest to us as gynecologists are aromatase inhibitors, depot medroxyprogesterone acetate, proton pump inhibitors, and gonadotropin-releasing hormone (GnRH) agonists.

Other medications that can affect BMD are glucocorticoids, unfractionated heparin, selective serotonin reuptake inhibitors, excessive amounts of thyroid replacement agents, and some antiseizure medications.

If you suspect a secondary cause of osteoporosis, be prepared to perform a basic workup that includes:

- a careful history and physical examination
- complete blood count
- a chemistry profile, including serum calcium, phosphorous, electrolytes, alkaline phosphatase, and creatinine.

In addition, measurement of 25-hydroxy vitamin D and thyroid-stimulating hormone (TSH) may be helpful, as may serum protein electrophoresis.

Patients who have clinical or laboratory abnormalities suggestive of a secondary cause of osteoporosis are usually referred to a metabolic bone specialist (endocrinology or rheumatology).

WHAT THIS EVIDENCE MEANS FOR PRACTICE

When a patient has any clinical history that suggests a secondary cause of bone loss other than menopause-related estrogen deficiency, simple laboratory tests are appropriate and may uncover a condition that necessitates referral to a metabolic bone expert.

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COMING IN DECEMBER 2012: Update on Urinary Incontinence
by Karen Noblett, MD, University of California–Irvine
Don't miss it!

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Quantitative ultrasound assessment of bone can help predict a woman's risk of fracture

Guglielmi G, Rossini M, Nicolosi MG, Tagno A, Lentini G, de Terlizzi F. Three-year prospective study on fracture risk in postmenopausal women by quantitative ultrasound at the phalanges [published online ahead of print August 15, 2012]. J Clin Densitom. doi:10.1016/j.jocd.2012.07.006.

Chan MY, Nguyen ND, Center JR, Eisman JA, Nguyen TV. Quantitative ultrasound and fracture risk prediction in non-osteoporotic men and women as defined by WHO criteria [published online ahead of print August 10, 2012]. Osteoporos Int. doi:10.1007/s00198-012-2001-2.

FAST TRACK

Calcaneal broadband ultrasound attenuation is an independent predictor of fracture risk in women who have nonosteoporotic BMD

I became interested in bone health through my longstanding interest in ultrasound, when a manufacturer asked me to evaluate equipment designed to assess bone density of the heel through quantitative ultrasound (QUS). This modality is not the diagnostic imaging we are familiar with in obstetrics and gynecology. In QUS, the homogeneity of healthy bone promotes sound transmission, whereas the voids and discontinuity of osteoporotic bone impede it. Therefore, normal bone has a faster speed of sound than less healthy bone. The other important quantitative measure is broadband ultrasound attenuation (BUA). Healthy bone is dense and absorbs and scatters sound to a greater extent than osteoporotic bone does.

Two trials of QUS

In 2010, Guglielmi and colleagues contacted 2,210 Italian women who had undergone QUS of the phalanges in 2006–2007. These women had an average age of 60.9 years, entered menopause at an average age of 49.3 years, and had a mean body mass index (BMI) of 26.5 kg/m^2. By 2010, this group had experienced 108 new major osteoporotic fractures, including 23 hip fractures and 56 vertebral fractures. Investigators found a statistically significant correlation between QUS findings and fracture risk.

Chan and colleagues focused on 312 women 62 to 92 years of age who had femoral neck BMD, as measured by DXA, of –2.5 or better. QUS was measured as BUA at the calcaneus. The incidence of any fragility fracture was ascertained by radiographic reports during the follow-up period from 1994 to 2011. Eighty women (26%) experienced at least one fragility fracture during follow-up. After adjustment for covariates, women were significantly more likely to experience any fracture if BUA was decreased (hazard ratio [HR], 1.50; 95% confidence interval [CI], 1.13–1.99).

When the models that included BUA were compared with those that used femoral neck BMD, they had a greater area under the curve (0.71, 0.85, 0.71 for any fracture, hip fracture, and vertebral fracture, respectively) and yielded a net reclassification improvement of 16.4% (P = .009) when combined with femoral neck BMD. These findings suggest that calcaneal BUA is an independent predictor of fracture risk in women who have nonosteoporotic BMD.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

In an era of increasing pressure to reduce costs, QUS assessment of bone is a promising modality that may be useful as a screening tool. Although it measures different variables than DXA imaging (more microarchitecture, less true density), it seems to predict the risk of fracture at less cost without ionizing radiation.

In the pipeline: A drug that curbs bone resorption without diminishing bone formation

Williams SC. Potential first-in-class osteoporosis drug speeds through trials. Nat Med. 2012;18(8):1158.

Ng KW. Potential role of odanacatib in the treatment of osteoporosis. Clin Interv Aging. 2012;7:235–247.

Alendronate was the first of the oral bisphosphonates to be approved by the US Food and Drug Administration (FDA). Once it was approved in 1999, the drug quickly became the most widely used bone agent in clinical practice and was soon joined by other oral and intravenous bisphosphonates. Regrettably, highly publicized adverse effects have caused many patients to shy away from this class of drugs. Two years ago, the FDA approved denosumab, a subcutaneous injectable agent that is a RANK ligand inhibitor.

The bisphosphonates and denosumab increase bone mass by shutting down the osteoclasts responsible for bone resorption, but they also inhibit creation of new bone. A new category of drug that inhibits the bone-resorption enzyme Cathepsin K appears to inhibit bone resorption without diminishing bone formation. Trials of two previous agents in this class were halted because of adverse effects—particularly effects to the skin, where the enzyme is expressed in addition to bone. However, Phase 2 trials in which odanacatib was compared with alendronate found that the new drug increased BMD almost twice as much as alendronate did, with less reduction in serum markers of bone formation.

Phase 3 trials of odanacatib in 16,000 women older than age 65 recently were halted so that the manufacturer could pursue regulatory approval ahead of the previous schedule. Although Phase 3 data have not been published yet, odanacatib may prove to be an exciting alternative to existing therapies.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Odanacatib is not yet available. However, by discussing therapies that may be "around the corner" with our patients, we demonstrate that we are staying ahead of the curve of scientific development.

FAST TRACK

Phase 2 trials found that odanacatib increased BMD almost twice as much as alendronate did, with less reduction in serum markers of bone formation

Other articles on bone health in recent issues of OBG MANAGEMENT

- **What is the optimal interval for osteoporosis screening in postmenopausal women before fracture occurrence and osteoporosis?** Steven R. Goldstein, MD (Examining the Evidence; August 2012)
- **An appeal to the FDA: Remove the black-box warning for depot medroxyprogesterone acetate!** Andrew M. Kaunitz, MD, and David A. Grimes, MD (Guest Editorial; August 2011)

They're available in the archive at obgmanagement.com