

# Treating and preventing osteoporosis

in the **wake**  
of **WHI**



■ BY ROBERT LINDSAY, MD, WULF UTIAN, MD,  
AND ROBERT WILD, MD, MPH

The recent findings regarding hormone replacement therapy aren't the only new developments on the osteoporosis front. Here, 3 experts discuss trends in prevention, diagnosis, and treatment, as well as what's on the horizon.

## OUR EXPERT COMMENTATORS:

**Robert Lindsay, MD**, is chief, internal medicine, Helen Hayes Hospital, West Haverstraw, NY; professor, clinical medicine, Columbia University, New York, NY; and board member, National Osteoporosis Foundation.

**Wulf Utian, MD**, is executive director, North American Menopause Society, Mayfield Heights, Ohio; consultant gynecologist, Cleveland Clinic Foundation, Cleveland, Ohio; and president, Rapid Medical Research, Cleveland, Ohio.

**Robert Wild, MD, MPH**, is professor and chief, reproductive endocrinology, adjunct professor of medicine and epidemiology, Oklahoma University Health Sciences Center, Oklahoma City, Okla.

In some respects, the estrogen-progestin arm of the Women's Health Initiative (WHI) offered hormone replacement therapy (HRT) advocates encouragement. While it is true that this particular study was terminated due to an increased number of events for breast cancer, heart attack, and stroke, it was also the first large-scale clinical trial to prove that HRT can reduce fracture occurrence.

Osteoporosis threatens the public health, particularly for women. According to the National Institutes of Health (NIH), of the 10 million Americans who suffer from osteoporosis, 8 million are women over the age of 50. In addition, an estimated 18 million women with low bone mass have yet to be diagnosed or treated.<sup>1</sup>

Still, this is not an irreversible trend. Thanks to recent educational efforts, many more Americans know how to prevent this disease. Advances in detection and treatment protocols, meanwhile, have given physicians new options for managing patients at risk.

As protectors of women's health, Ob/Gyns have the unique opportunity to provide patients with the information they need

to achieve and maintain optimal bone mass, as well as to ensure that proper preventive measures start early in life. Here, 3 experts review recent advances in the field of osteoporosis, and offer guidance for effective prevention and treatment.

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## KEY POINTS

- Hormone replacement therapy is a viable option for the prevention of osteoporosis.
- The US Preventive Services Task Force recently recommended that women over the age of 65 get a bone densitometry test.
- Although bone loss is a side effect of depot medroxyprogesterone acetate (DMPA) injections and gonadotropin-releasing hormone agonists (GnRH), physicians should not halt therapy in women for whom these agents are indicated.
- Data suggest that the current vitamin D recommendation of 400 to 800 IU daily is probably inadequate.
- Many physicians need further education on the use of dual-energy x-ray absorptiometry.

### **HRT and osteoporosis**

**OBG Management:** In light of the WHI findings, women at an increased risk for osteoporosis may be more likely to forego HRT. Are there better agents than HRT for preventing osteoporosis?

**Wild:** The WHI was a well-done clinical trial that had the advantage of recruiting a large number of women. Its endpoints included a favorable effect on fracture prevention. However, in view of the deleterious effects of this particular estrogen-progestin combination, the risk-benefit ratio may not be favorable for chronic disease prevention for more than 4 years in older women. But this question is still open as we await the results of the WISDOM trial, a large scale clinical trial in the United Kingdom using similar agents and evaluating similar clinical endpoints as in the WHI.

While HRT does remain a good choice, fortunately, many other therapies to prevent osteoporosis and its consequences are available (TABLE). Many patients, particularly older women without estrogen-deficiency symptoms, are good candidates for raloxifene, bisphosphonates, and selective estrogen receptor modulators (SERMs) soon to be on the market. It really depends on an individual's needs. Unfortunately, we do not have

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any long-term data on the use of bisphosphonates in younger women. Some animal data have given cause for concern, at least theoretically, that the protective effects of these agents will not continue after several years of use.

**Lindsay:** Women have been drifting away from HRT for quite some time, particularly for long-term use in preventing osteoporosis.

But it's important to realize that the WHI was a very large and powerful study that demonstrated a fracture benefit in people who were not selected because they had osteoporosis. Research on other anti-osteoporosis agents has shown no reduction in fracture risk for people who do not have osteoporosis. This means that HRT is a viable option for the prevention of osteoporosis, regardless of the other issues surrounding it. I think it will remain one of the agents we're likely to use.

**Utian:** I agree with Dr. Lindsay. What's interesting is that the breast cancer increase reported in the WHI study was not statistically significant, but the rate of fracture reduction was. If we actually look at the WHI and the Heart and Estrogen/Progestin Replacement Study (HERS)—2 very large, randomized studies that have caused this antihormone brouhaha—we are certainly dealing with older women exclusively. I'd be interested to hear what Dr. Lindsay has to say about a woman who is under 50 with significant osteoporosis risk. Would he put her on a long-term bisphosphonate or would he prefer that younger women take HRT for the short-term and then consider some therapeutic change?

**Lindsay:** Generally, my prescribing pattern is to utilize HRT in younger women. Or, if the patient is asymptomatic and between the ages of 55 and 60, I might consider a tissue-selective estrogen like raloxifene. I would retain the bisphosphonates for women who are a bit older. In fact, many of the women who participated in the WHI would probably be the sort of candidates I would place on bisphosphonates, not HRT.

**OBG Management:** How long would you prescribe HRT to the younger woman?

**Lindsay:** One concept we've moved away from in the past 5 to 10 years is HRT forever. I think most physicians are prescribing HRT for 6 months to a year, until the patient's next appointment. At that point we review whether or not this is a beneficial medicine for that particular woman.

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**TABLE**

**Preserving bone: the 4 main options<sup>2</sup>**

<b>MEDICATION</b>	<b>BEST FOR...</b>	<b>STUDIES HAVE FOUND...</b>	<b>SIDE EFFECTS</b>
Bisphosphonates	Women who have already lost a significant amount of bone and are at high risk of developing osteoporosis  Postmenopausal women with osteoporosis	Alendronate reduces the risk of vertebral and hip fractures by 50% <sup>3</sup>  Risedronate reduces spine fractures by 40% to 50% <sup>4</sup>	Nausea, abdominal pain, loose bowel movements  Alendronate is associated with a small risk of ulcers in the esophagus
Selective estrogen receptor modulators	Preventing osteoporosis in postmenopausal women	Total bone mineral density was increased by 2.4% after 24 months of daily raloxifene use (60 mg) <sup>5</sup>  After 2 years, there was up to a 52% reduction in vertebral fractures when compared to women taking only calcium and vitamin D <sup>5</sup>	Leg cramps, hot flushes, increased risk of blood clots
Calcitonin	Treating osteoporosis in women who are at least 5 years postmenopausal	Reduces the risk of new vertebral fractures by 36% in patients with 1 to 5 previous fractures <sup>6</sup>	Nasal dryness, swelling of nasal membranes
Hormone replacement therapy	Women entering menopause with several risk factors for osteoporosis  Women with early or surgical menopause	A 34% reduction in the risk of hip fractures <sup>7</sup>  A 23% reduced risk in total osteoporotic fractures <sup>7</sup>	Depression, headaches, breast tenderness, premenstrual syndrome, skin irritation, weight gain

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### Decreasing fracture risk

**OBG Management:** There are more than 1.5 million osteoporosis-related fractures annually, with 33% of postmenopausal women sus-

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taining vertebral fractures. Is there any hope of these statistics decreasing? How so?

**Wild:** This is a better time than ever. Prevention is becoming a buzzword. The media is alerted. The key is education and affordability. We need to make concerted efforts to educate and alert underserved populations—particularly minority groups—that this disease can be silent.

**Lindsay:** I agree. I definitely think with better education of the aging population in terms of calcium and vitamin D intake, and physical activity, the rate of osteoporosis will decline. Not to mention the number of options for both prevention and treatment.

In addition, the increased availability of dual-energy x-ray absorptiometry (DEXA) has made it easier to diagnose individuals before they have a fracture. That is the point at which you get the maximum benefit from a therapeutic intervention.

**Utian:** The impact that organizations like the National Osteoporosis Foundation have had on creating awareness among the population is incredibly important. Last month the US Preventive Services Task Force also urged women 65 and older to get a bone densitometry.<sup>8</sup> Thanks to such efforts, I think we will see a decrease in osteoporosis.

### DMPA, GnRH, and bone loss

**OBG Management:** Recently, studies have noted bone mineral density (BMD) loss with

the use of depot medroxyprogesterone acetate (DMPA) injections and gonadotropin-releasing hormone agonists (GnRH). Do you find this to be true? If so, should women stop using these agents?

**Wild:** We now have adequately designed controlled studies to show that bone loss can occur with these 2 agents.<sup>9,10</sup> However, they still are useful for specific situations. We now have ways to prevent the associated bone loss if these medications are indicated. Treatments can be tailored to any given clinical situation. Alternate therapies can be used if monitoring shows significant bone loss. If DMPA and GnRH are indicated, then short courses are encouraged, with the use of concomitant agents when necessary.

**Lindsay:** These drugs are used for very specific indications. DMPA is used as a contraceptive; GnRH is used to suppress pituitary ovarian function, often in people with malignancies. Bone loss is a side effect of these agents. But that doesn't mean a woman should stop taking them. God forbid you tell a 25-year-old she has to stop DMPA because she might be losing bone, and she gets pregnant! You take action to prevent the loss of bone rather than halt the use of DMPA.

**OBG Management:** How do you take action?

**Lindsay:** That's really going back to the Holy Grail of osteoporosis prevention, which is adequate calcium, good nutrition, and physical activity.

**OBG Management:** Do DMPA and GnRH cause significant bone loss?

**Lindsay:** It depends on how long you're on them. If they're used for the short term, bone loss is reversible. If they are used for the long term, you've essentially turned that individual into a postmenopausal woman, and she'll lose bone. I would only prescribe these 2 agents for 18 months or so. Any longer than that, I would measure her bone density and the rate of bone turnover. If I thought she was at risk for significant osteoporosis, I would intervene with an osteoporosis-specific medication.

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**Utian:** In fact, women with endometriosis typically take GnRH no longer than 9 months. After 9 months, according to some reasonable studies, add-back estrogen therapy may not interfere adversely with the endometriosis.

**OBG Management:** What about women with a family history of osteoporosis? Would you still recommend DMPA or GnRH?

**Lindsay:** I wouldn't do much differently unless they would be using the therapy over the long term. In that case, I might measure bone density just in case, but I'd probably just follow her progress for the first year.

### Calcium and vitamin D

**OBG Management:** What is the role of calcium and vitamin D in the prevention of osteoporosis? Do they have a role in treatment?

**Wild:** They each have an essential role in treatment and prevention. Doses should be adjusted based on age and intervening conditions, e.g., when malabsorption or inadequate vitamin D exposure is problematic, including women over 65 who are bedridden or suffer from specific gastrointestinal disorders that affect absorption or transit time.

**Lindsay:** There is no doubt that taking an adequate amount of calcium reduces the risk of vertebral and, probably, hip fractures. The

fracture risk. There seems to be a threshold effect: If you're below a certain amount, you have an increased fracture risk. If you're above that, the risk goes away. That threshold is probably around 800 to 1,000 mg per day.

Now, the evidence surrounding vitamin D intake is a bit more circumstantial. The data suggest that we actually need more vitamin D as we get older, and that the current recommendation of 400 to 800 IU is probably inadequate. What you want to do is retain a serum level of vitamin D—25 hydroxy of vitamin D, to be specific. The normal range is 5 to 55 hydroxy. We now realize that the bottom end of that range includes people who are subclinically vitamin D deficient.

**Utian:** I really don't think that calcium and vitamin D on their own would be an effective treatment strategy. I wish it were that easy. They must be coupled with another therapy to truly make a difference.

### Appropriate use of densitometry

**OBG Management:** The use of dual-energy x-ray absorptiometry (DEXA) has led to real progress in the diagnosis of osteoporosis. What other sorts of diagnostic and preventive measures do you foresee?

**Lindsay:** The use of DEXA has led to a variety of innovative techniques to look not only at bone density, but at the architecture and quality of bone. These techniques include micro-computed tomography (CT), which actually can look in vivo at peripheral bone, and the development of CT technologies that will allow for the same sort of architectural examination of the spine and hip. Those are likely to come online within the next 5 years.

I also think that we'll learn how to better use the tools we currently have (that includes peripheral densitometry as well as DEXA), which means we'll get greater clinical utility from existing diagnostic studies.

**Utian:** I think it's not so much a matter of developing new tests or using DEXA to diagnose osteoporosis. Rather, the issue is, in clin-

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current recommendation from the federal government is about 1,200 mg of calcium per day, which is an average intake. It needs to be somewhere between 1,000 and 1,500 mg. There is no evidence that boosting calcium intake beyond 1,500 mg will further reduce

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ical practice, the major misunderstanding and potential abuse of DEXA in following up patients. The problem originates with practi-

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tioners who don't understand the results or know when to modify therapies. Few physicians understand the issues of precision and sensitivity with densitometry. They'll see a 1% to 2% change one way or the other and think that's reason enough to change a woman's therapy. Essentially, Ob/Gyns need to be a little more educated in what the numbers and T-scores really mean. I don't know if you agree, Dr. Lindsay.

**Lindsay:** I completely agree. There needs to be some sort of clinical rationalization of how we're using DEXA. We currently obey the Medicare guidelines, which say repeat measurements should be made every 2 years. And that's without any great rationale.

We're also beginning to see the development of anabolic agents, which will lead to much larger gains in bone mass and bone density that are apparent far earlier than 2 years. We basically need some sort of nationwide quality-control system akin to what was put in place for mammography.

**Wild:** Certainly, Dr. Lindsay and Dr. Utian can give better specifics, but there are 2 concepts I would like to get across. First, I think we need a push toward inexpensive methods of detection that offer adequate sensitivity, specificity, and positive predictive values. More important is increasing the number of people who are screened, even with imperfect tools, then evaluating them in depth using

more sophisticated methods. This first-line, second-line approach will allow us to detect the large portion of women who are asymptomatic and can benefit greatly from prevention therapies.

**OBG Management:** When should physicians conduct a bone densitometry test?

**Lindsay:** When a woman is estrogen deficient or is in the process of becoming estrogen deficient. It's nice that the Preventive Services Task Force recommended that women 65 and older should get tested. But I think we are moving on from that, toward a future of assessing the younger woman's skeletal status. ■

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