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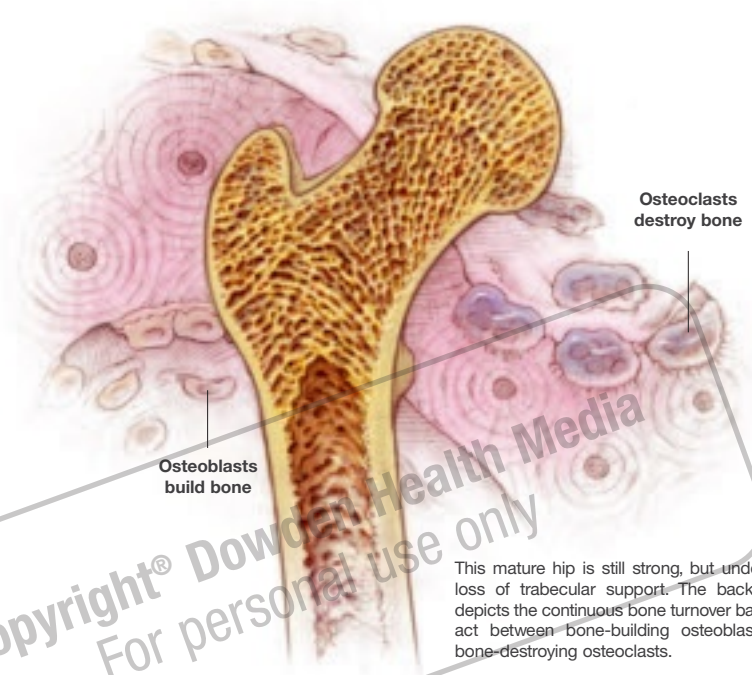

This mature hip is still strong, but undergoing loss of trabecular support. The background depicts the continuous bone turnover balancing act between bone-building osteoblasts and bone-destroying osteoclasts.

Real-life risks and benefits of fracture-reducing drugs

How do the high-profile studies of 2006 apply to our patients?

IN THIS ARTICLE

It is all too easy to focus on T-scores and lose sight of why we check bone mass: we want to prevent fragility fractures—not osteoporosis per se. Fracture *incidence* is greater in women with osteoporosis, but the *absolute* number of fragility fractures is far greater in the women who have not yet reached that threshold. That was my main message last year. It still is, although I had hoped we would by now have in our hands a fracture risk assessment tool due from the World Health Organization. It will use age, DXA score, history, and other factors to project 5- and 10-year risk of fracture. Then we will simply have to decide at what level of risk, for an individual patient, drug therapy is indicated. Watch this space!

What's new in 2006

1. **Osteonecrosis of the jaw:** What clinicians need to know
2. **Raloxifene:** A bone drug that reduces new onset breast cancer
3. **Estrogen for bone protection:** Time for a comeback?
4. **Risedronate:** Not just for fracture prevention?

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1 Osteonecrosis of the jaw: What clinicians need to know

Woo SB, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med. 2006;144:753–761.

- Patients with multiple myeloma and metastatic carcinoma to the skeleton who were receiving intravenous nitrogen-containing bisphosphonates are at greatest risk for osteonecrosis of the jaws; these patients represent 94% of published cases

This was the year of massive media attention on bisphosphonate therapy and osteonecrosis of the jaw. A bone specialist I know said he got even more phone calls after this report was published than after the WHI blitz 4 years ago.

Patients started calling when the lay press limelight focused on a report by Woo et al, who reviewed all of the world's literature published since 1966, and identified 368 reported cases of bisphosphonate-associated osteonecrosis of the jaw (ONJ).

Main findings

Of the 368 cases, 94% were being treated with intravenous bisphosphonate therapy; 85% of the patients had either multiple myeloma or metastatic cancer of the breast. More than half of all cases (60%) were preceded by tooth extraction or other dentoalveolar surgical procedure to treat infections, and the remaining 40% were related to infection, denture trauma, or other physical trauma.

The latter group of cases occurred spontaneously, although the patients affected often wore dentures. The mandible was more commonly affected than the maxilla by a ratio of 2:1.

Other studies have reported 75% of patients with ONJ were receiving chemotherapy at the time of diagnosis, and 38% were on corticosteroids.

Do these findings affect prescribing?

A small number of cases of ONJ in postmenopausal women taking oral bisphosphonates have occurred, though rarely—well under 1 per 100,000 patients treated.

Realize that patients with myeloma or metastatic breast cancer are usually treated with high-dose, high-potency intravenous bisphosphonate.

There were no reports of ONJ in any of the controlled trials on use of bisphosphonates for osteoporosis; this represents more than 60,000 patients who in some cases were treated for more than 8 years.

Recommendations

The American Society for Bone and Mineral Research advises:

- Ongoing dental care for patients on bisphosphonates does not differ from that in the general population
- Before starting bisphosphonate therapy, patients should have a dental examination and should complete required dental procedures. (Preventive strategies include removing all foci of dental infection before starting bisphosphonate therapy [Woo et al].)
- Bisphosphonates need not be discontinued prior to dental procedures
- The low risk of ONJ in the context of dental procedures should be explained to patients
- Dental surgery should be conservative in patients on bisphosphonates

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There were no reports of ONJ in any of the controlled trials on use of bisphosphonates for osteoporosis

KEY REPORTS

Migliorati CA, Siegel MA, et al. Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. Lancet. 2006;7:508–514.

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Van den Wyngaert T, Huizing MT, et al. Bisphosphonates and osteonecrosis of the jaw: cause and effect or post hoc fallacy? Ann Oncol. 2006;17:1197–1204.

CONTINUED

2 Raloxifene: An osteoporosis drug that reduces new onset breast cancer

Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes. The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. JAMA 2006;295:2727-2741.

- Raloxifene is as effective as tamoxifen in reducing risk of invasive breast cancer and has a lower risk of thromboembolic events and cataracts. The risk of other cancers, fractures, ischemic heart disease, and stroke is similar for both drugs

Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med. 2006;355:125–137.

- Although there was no reduction in CHD, there was no increase, unlike the estrogen and progesterone arm of the Women's Health Initiative (WHI). Additionally, however, there was a 44% reduction in invasive breast cancer.

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2 large trials cause me to believe that raloxifene reduces new onset breast cancer in virtually every group studied

Two large trials cause me to believe that raloxifene significantly reduces new onset breast cancer in virtually every group of women in which it has been studied.

Why you didn't hear about this until now

Raloxifene was FDA-approved for *prevention* of osteoporosis in 1997 and for *treatment* of osteoporosis in 1999. There was a statistically significant 76% reduction in new onset breast cancer in raloxifene-treated patients versus placebo through 4 years of the MORE (Multiple Outcomes of Raloxifene Evaluation) trial, and this persisted at a 66% reduction through the additional years of the CORE (Continued Observation of Raloxifene Evaluation) trial.

Findings effectively buried. However, because of the wording of the FDA label, and, as a result of a $36 million fine from the Department of Justice, for promotional activities in the early years after its release, these findings were effectively buried and not well promulgated.

STAR and RUTH trials

Study of Tamoxifen and Raloxifene

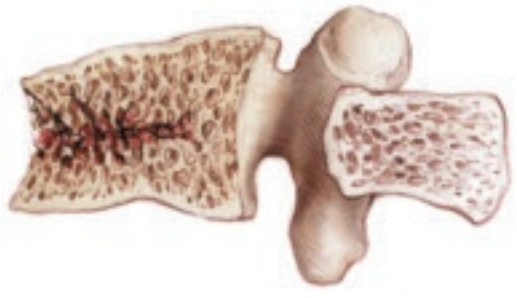
The STAR trial reported by Vogel et al involved 19,747 postmenopausal women enrolled on the basis of their high risk for breast cancer. The patients were randomized to tamoxifen (already approved for breast cancer prevention) or raloxifene.

Over 5 years of study, the incidence of invasive breast cancer was virtually identical in both groups. However, the raloxifene group had statistically significant lower numbers of thromboembolic events, cataracts, hysterectomies performed, and endometrial hyperplasias. A 38% reduction in endometrial cancer in the raloxifene group had not reached statistical significance but was trending in that direction.

Raloxifene Use in The Heart

The RUTH trial reported by Barrett-Connor et al involved 10,101 postmenopausal women selected for multiple risks for coronary heart disease.

Although there was no reduction in coronary heart disease, there was no increase, unlike the estrogen and proges-



Studies of fracture reduction in populations with existing osteoporosis include the Fracture Intervention Trial, which enrolled women with low bone mass and existing vertebral fractures. Clinical vertebral and other fractures were substantially reduced in the treatment group

terone arm of the Women's Health Initiative (WHI). Additionally, however, there was a 44% reduction in invasive breast cancer (95% CI 0.38–0.83). Remember, these women were chosen for their risk of heart disease. The rate of breast cancer in the placebo group was 2.7 cases per 1,000 women per year, and thus the 44% reduction means the rate in the treatment group was 1.5 cases per 1,000 women per year.

Consider the context

For comparison purposes, consider an average-risk group in the WHI, where the incidence of breast cancer was 3.3 cases per 1,000 women per year. Contrast this rate to that of a high-risk group, such as the placebo group in the original breast cancer prevention trial (BCPT), where the incidence was 6.8 cancers per 1,000 women per year.

A case in point

I believe that such information must be available to clinicians and must be factored into your decision when contemplating a bone drug. A recent anecdote underscores the problem.

DXA T-score of -2.0 in the hip and atypical ductal hyperplasia

An internist called me to discuss a mutual patient whom I had placed on raloxifene 2 years earlier. His comment was that raloxifene does not work in the hip. Our mutual patient had a T-score on DXA in the hip of -2.0 and in the spine of -0.7 (falsely improved by some osteophytes). In addition, she had been diagnosed with atypical ductal hyperplasia of the breast 2 years earlier.

I pointed out to him that studies of hip fracture reduction with bisphosphonate were all performed in women with osteoporosis. Furthermore, after the NHANES III correction, a sizable number of women in the MORE trial were not osteoporotic. In fact, the fracture incidence in the MORE trial *placebo* group was 0.7%—an extremely low risk—compared with 2.2% in the *treatment* group in the Fracture Intervention Trial I, and 3.0% in the *treatment* group in the Hip Intervention Program.

Stated another way, the incidence of hip fracture in the MORE placebo group was less than that in the treated groups in the Fracture Intervention Trial I and the Hip Intervention Program.

But perhaps the most important point in my anecdotal case is that the woman had a diagnosis of atypical ductal hyperplasia of the breast, a lesion that significantly increases her risk of invasive breast cancer. For these reasons, raloxifene was a much better choice for her fracture reduction pharmacotherapy. Her internist was unaware of these breast effects and had not taken this into account.

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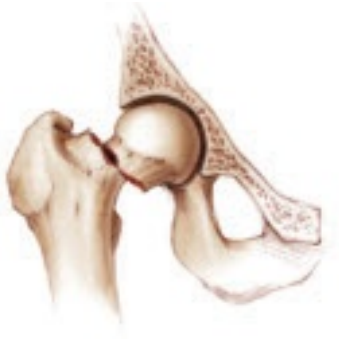
Raloxifene was a good choice as the fracture reduction agent for a woman with atypical ductal hyperplasia



4 out of 10 Caucasian women over age 50 will fracture a hip, spine, or wrist sooner or later

1 of every 5 who fracture a hip ends up in a nursing home

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CONTINUED

3 Estrogen for bone protection: Time for a comeback?

Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA. 2006;295:1647–1657.

- Treatment with conjugated equine estrogen (CEE) alone for 7.1 years does not increase breast cancer incidence in postmenopausal women with prior hysterectomy. However, treatment with CEE increases the frequency of mammography screening requiring short interval follow-up. Initiation of CEE should be based on consideration of the individual woman's potential risks and benefits

Jackson RD, Wactawski-Wende J, LaCroix AZ, et al. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the Women's Health Initiative randomized trial. J Bone Miner Res. 2006;6:817–828.

- CEE reduces the risk of fracture and increases bone mineral density in hysterectomized postmenopausal women

It may be time to revisit our initial reaction to the WHI. Although most estrogens are FDA-approved for treatment of osteoporosis, recommendations since the WHI have generally been that we should reserve hormone therapy or estrogen therapy for disruptive transitional symptoms (hot flashes, night sweats, etc.), and prescribe the lowest dose possible for the shortest time possible, consistent with the patient's treatment goals.

Rethink therapy for 2 types of patients?

Recent reports, however, may cause us to rethink that approach, especially in 2 types of patients:

- **hysterectomized women** who will be treated with estrogen only
- **women with a uterus** who can safely be managed on estrogen only, without progestogen, by incorporating transvaginal ultrasound monitoring

Stefanick et al reported on the 10,739 women aged 50–79 in the estrogen-only arm of the WHI, who received placebo or 0.625 mg of conjugated equine estrogen. After a mean follow-up of 7.1 years, there were 104 cases of invasive breast cancer in this CEE group and 133 cases in the placebo group.

Stated another way, this represents a 20% reduction in breast cancer in women in the CEE group. Although this reduction was not statistically significant, it is in stark contrast with the increase in breast cancer seen in numerous studies of estrogen and progestogen together.

Women in the WHI had all levels of fracture risk

Jackson et al also analyzed fracture incidence in the WHI E2-only arm, as assessed by semiannual questionnaires and verified by adjudication of radiology reports.

Women on CEE had statistically significant reductions in hip fracture (35%), clinical vertebral fracture (36%), wrist fracture (42%), and total fractures (29%), compared with placebo. This trend held across all levels of fracture, although the reductions were greatest in patients at highest risk.

This is notable, however, because the WHI was primarily studying the effect of

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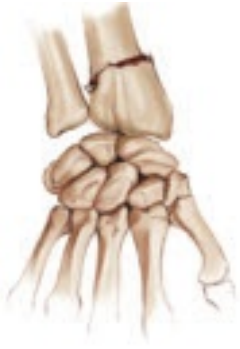
With transvaginal ultrasound monitoring, some women with a uterus can be managed on estrogen only



Statistically significant reductions in fracture, compared with placebo, in the WHI E2-only arm were:

wrist 42%
clinical vertebral 36%
hip 35%
total fractures 29%

CEE on coronary heart disease. Unlike virtually all osteoporosis studies, in which women with increased risk of fracture are studied, the women selected for the Women's Health Initiative represent all levels of fracture risk—and this placebo-controlled, large, randomized study discovered that all fractures, across all levels of risk, were significantly reduced. And there was no increase in breast cancer.

This may well weigh in on many a clinician's thought process about indications and real risks of estrogen therapy.

KEY REPORTS

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Watch for
UPDATE URINARY INCONTINENCE *in December*

Anne M. Weber, MD
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In every issue's UPDATE, an expert reviews the decisive studies, emerging clinical issues, and new drugs, devices, and techniques that are changing patient care.

4 Risedronate: Not just for fracture prevention?

Buckland-Wright JC, Messent EA, Bingham CO III, et al. A 2 yr longitudinal radiographic study examining the effect of a bisphosphonate (risedronate) upon subchondral bone loss in osteoarthritic knee patients. Rheumatology (Oxford). 2006 Jul 11; [Epub ahead of print].

- This preliminary study showed that patients with marked cartilage loss receiving risedronate 15 mg/day retained vertical trabecular structure, and those receiving risidronate 50 mg/week increased vertical trabecular number, thereby preserving the structural integrity of subchondral bone in knee osteoarthritis

Bone formation in osteoarthritic knees reversed disease-related bone loss while maintaining structural integrity within the subchondral cancellous bone in patients treated with risedronate, in this 2-year study. Patients with progressive knee osteoarthritis were enrolled in this double-blinded, multicenter, randomized, placebo-controlled trial.

The treatment groups included placebo, risedronate 5 mg/day, 15 mg/day, and 50 mg/week. Patients receiving risedronate 15 mg/day retained vertical trabecular structure and those receiving 50 mg/week increased vertical trabecular number, thereby preserving the structural integrity of the subchondral bone.

This is important because weakening and loss of vertical trabecular support, when combined with the biomechanical weakening of the bone due to disease-related reduction in mineral content, are believed to contribute to collapse of the tibial compartment in late-stage osteoarthritis. It has been suggested that bisphosphonates are associated with decreased bone formation as an expected consequence of suppressing the coupled bone remodeling process. This did not appear to be the case in this study. In fact, the study tends to agree with experimental work that shows that high doses of bisphosphonates, as well as repeated administration, may enhance bone accretion. ■

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High doses of bisphosphonates appeared to enhance bone accretion

KEY REPORTS

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The author serves on the advisory boards for Eli Lilly, Merck, Pfizer, Procter & Gamble, and GlaxoSmithKline.