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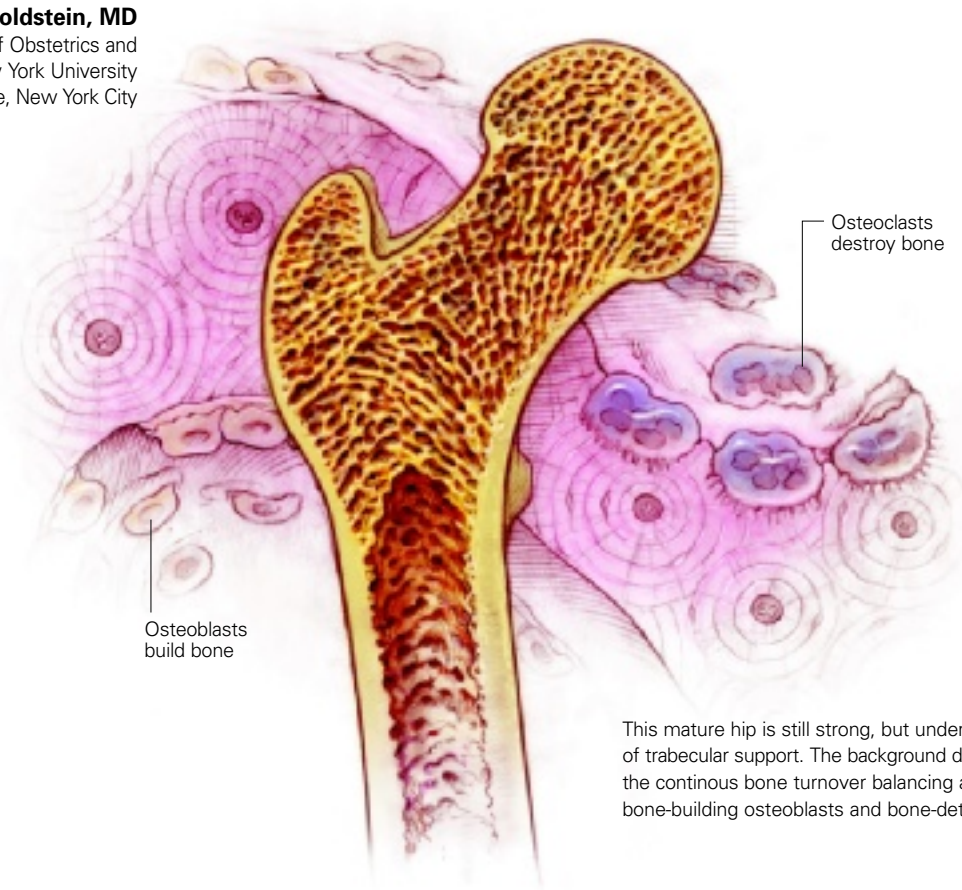

This mature hip is still strong, but undergoing loss of trabecular support. The background depicts the continous bone turnover balancing act between bone-building osteoblasts and bone-detroying osteoclasts.

IN THIS ARTICLE

Preventing fragility fractures
Effective drugs and doses

The latest data from well-designed trials, including FACT, CORE, and MOBILE, have enlightened us on efficacy, tolerability, and patient-friendly dosing of antiresorptive drugs

It is all too easy to focus on T-scores and lose sight of why we are measuring women's bone density. We are not trying to prevent osteoporosis; we are trying to prevent the fractures that result from osteoporosis.

The numbers tell why. The total number of fragility fractures in American women in a single year—1 million—outnumbers all heart attacks, strokes, breast cancers, and gynecologic cancers combined. A quality-of-life study by Toteson and Hammond found that 4 out of 10 Caucasian women over 50 will fracture a hip, spine, or wrist, sooner or later. One of every 5 who fracture a hip ends up in a nursing home. The direct care cost of osteoporotic fractures was $17 billion in 2001 dollars.

Now, we have more treatment options than ever. And 2005 has been a banner year for discoveries we can put into practice immediately, in our efforts to prevent fragility fractures.

COVER IMAGE: SCOTT BODELL

Why so confusing?

McClung MR. The relationship between bone mineral density and fracture risk. Curr Osteoporos Rep. 2005;3:57–63.

- The terms osteopenia and osteoporosis are arbitrary cutoffs. Fracture risk is a continuum and involves multiple factors in addition to bone mass.

Osteoporosis: A skeletal disease characterized by low bone mass and disruption of bone tissue architecture that results in a reduction in the mechanical strength of the skeleton, increasing the risk of fragility fractures."

The clinically crucial part of that definition is … *"increasing the risk of fragility fractures."* Certainly, low bone mass on DEXA is a risk factor. And guidelines from the World Health Organization (WHO), the National Osteoporosis Foundation, and the North American Menopause Society are based on T-scores. However, treatment that bases intervention on absolute fracture risk would be much more appropriate; in fact, the WHO is expected to shortly issue a method to calculate fracture risk. Factors are likely to include age, previous fracture, family history, body mass index, ever use of steroids, propensity for falling, eyesight, overall health, and bone mass (ie, BMD determinations).

We need to realize that WHO definitions of T-score categories are meant for postmenopausal women. Inappropriate use of DEXA scanning in a premenopausal patient may identify a woman with low bone mass, but her bone quality and risk of fragility fracture differ greatly from that of a distantly postmenopausal woman with the same T-score. It may seem counterintuitive, but a 50-year-old woman with a T-score of –3.0 has the same absolute fracture risk, going forward, as an 80-year-old woman with a T-score of –1.

Although the risk of fracture is greatest in women with osteoporosis, there are many more women with osteopenia who will have a fracture. But that doesn't mean we should prescribe pharmacotherapy for every osteopenic woman in an attempt to prevent fractures. As the US Surgeon General's report last October estimated, 34 million women have osteopenia and "only" 10 million have osteoporosis. Not every woman with osteopenia should be a candidate for pharmacotherapy, but these facts do underscore the need for a better way to assess absolute fracture risk.

ADDITIONAL REFERENCES

Miller PD, Barlas S, Brenneman SK, et al. An approach to identifying osteopenic women at increased short-term risk of fracture. Arch Intern Med. 2004;164:1113–1120.

Salkeld G, Cameron ID, Cumming RG, et al. Quality of life related to fear of falling and hip fracture in older women: a time trade off study. BMJ. 2000;320:341–346.

Schuit SC, van der Klift M, Weel AE, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone. 2004;34:195–202.

Tosteson AN, Hammond CS. Quality-of-life assessment in osteoporosis: health-status and preference-based measures. PharmacoEconomics. 2002;20:289–303.

Are all bisphosphonates created equal?

Rosen CJ, Hochberg MC, Bonnick SL, et al. Postmenopausal osteoporosis: a randomized double-blind study. J Bone Miner Res. 2005;20:141–151.

- Antifracture efficacy at the spine appears to be indistinguishable among antiresorptive agents, despite differences in BMD and bone turnover. Gastrointestinal tolerability was similar in the FACT study.

The FACT study (Fosamax Actonel Comparison Trial) found wide variations in 2 surrogate endpoints—BMD and bone turnover markers—but unfortunately was not powered to compare fracture reduction, which is the clinically relevant endpoint. This head-to-head trial comparing once-weekly risedronate (Actonel) and alendronate (Fosamax) in postmenopausal women with low BMD was designed to evaluate changes in BMD and bone turnover markers. Upper GI tolerability was also compared, and was found

FAST TRACK

Treatment success is the absence of bone loss, not extent of bone gain

FAST TRACK

The Fosamax Actonel Comparison Trial evaluated BMD and bone turnover, not fracture reduction

to be similar for both drugs. The double-blind, randomized, active-controlled study was conducted at 78 US sites and involved 1,053 patients. Postmenopausal women with a bone density T-score more than 2.0 standard deviations below the young normal mean bone mass were given 70 mg once-weekly alendronate or 35 mg once-weekly risedronate. The only exclusion criterion regarding previous GI symptoms was any abnormality of the esophagus that might delay esophageal emptying.

Endpoints of the FACT study. The primary endpoint was change from baseline BMD at the hip trochanter at 12 months. Secondary endpoints included BMD at multiple sites, bone turnover markers, and drug tolerability. After 12 months, BMD increased 3.4% with alendronate and 2.1% with risedronate ($P<.001$). Alendronate produced significantly greater reductions in bone markers. Fracture data were collected as part of the safety monitoring: 26 fractures in the alendronate group and 20 in the risedronate group.

Antiresorptives lower fracture risk even without increasing BMD

However, until a head-to-head antifracture efficacy study is done, we cannot infer whether alendronate or risedronate is more effective, based on surrogate endpoints. In fact, if one looks at observations on calcitonin and raloxifene, all 4 drugs provide a similar level of fracture protection, at least in the spine, despite marked differences in turnover markers and BMD. This similarity in antifracture efficacy is probably because antiresorptive drugs affect bone quality and microarchitecture, as well as bone mass.

Antiresorptive medications reduce fracture risk, even in the absence of substantial increases in BMD. This finding has significant implications for monitoring therapy. The misconception that efficacy depends on the amount of bone gained often prompts physicians to stop a drug or add a second drug if a patient's bone density does not increase. The indication of treatment success, however, is absence of bone loss, not extent of bone gain.

The key to meaningful monitoring

Serial observations with DEXA scanning are fraught with error if one does not understand the concept of least specific change. Least specific change is defined as 2.77 times the precision error of the scanning machine used. Thus, in good centers, BMD measurement of the spine should vary no more than ±3%; measurement of the hip may vary as much as ±5%. For example, a patient who gains 2% over time in the hip and spine is no different statistically from a patient who loses 2% over time in the hip and spine. However, many patients and clinicians feel gratified by a modest increase—and consider an alternative or additional medication if there is a mild decrease. If we take into account the "least specific change," it becomes evident that in both cases, the patients are in fact unchanged.

Daily pill more likely to get blamed for GI symptoms?

The perception among many clinicians prior to the FACT head-to-head trial was that risedronate had greater GI tolerability than alendronate. However, in the FACT trial no differences were noted in adverse events of the GI tract for either compound. When first introduced, alendronate was a daily regimen. Both alendronate and risedronate are now being given once per week, predominately, and it seems that this schedule has led to fewer complaints and fewer patients discontinuing medication because of GI symptoms. This change probably is because patients are not as likely to relate all of their GI symptoms to a pill taken a week ago, but are more likely to blame any GI complaint on a pill they take every day.

ADDITIONAL REFERENCES

Bauer DC, Black DM, Garnero P, et al for the Fracture Intervention Trial Study Group. Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the Fracture Intervention Trial. J Bone Miner Res. 2004;19:1250–1258.

Watts NB, Cooper C, Lindsay R, et al. Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. J Clin Densitom. 2004;7:255–261.

Which is better, once-a-month or once-a-day ibandronate?

Miller PD, McClung MR, Macovei L, et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. J Bone Miner Res. 2005;20:1315–1322.

"Monthly ibandronate is at least as effective and well tolerated as . . . the daily ibandronate regimen in postmenopausal osteoporosis."

So concluded the investigators in the MOBILE study, which compared the efficacy and safety of monthly and daily oral ibandronate (Boniva). It is the first bisphosphonate the Food and Drug Administration (FDA) has approved for once-a-month dosing. Since its approval last March, there seems to be a firestorm of activity either promoting or challenging its use.

Which schedule will patients follow?

Virtually all clinicians would agree that patients prefer weekly to daily dosing, especially if the medication is somewhat inconvenient. Bisphosphonates should be taken with a full glass of water, and the patient should remain standing or sitting upright and avoid other food or drink for 1/2 hour (a full hour with ibandronate).

It remains to be seen. Once-a-month dosing may offer more appeal than weekly alendronate or risedronate, but whether adherence will be better or worse remains to be seen.

Does ibandronate prevent fractures?

Daily ibandronate, 2.5 mg, has been shown to improve bone density and bone turnover values and to reduce vertebral fractures.

There are no prospective data showing nonvertebral fracture reduction—as there are for alendronate and risedronate. However, there was a time when we had only vertebral fracture data on those compounds; a leap of faith was necessary to prescribe them for overall fracture prevention.

The MOBILE study employed a randomized, double-blind method referred to as a "noninferior" trial. A total of 1,609 women with osteoporosis were assigned to once-monthly or daily oral ibandronate. All monthly regimens proved "noninferior" to daily dosing, and the highest monthly dose (150 mg) proved superior to the daily regimen, in terms of lumbar spine BMD increase at 1 year. All regimens were similarly tolerated.

Those who would criticize this methodology will be interested to recall that noninferiority trials were exactly the mechanism that led the way from daily to weekly dosing for alendronate and risedronate.

Which patients are best suited to ibandronate?

Until nonvertebral fracture data become available, however, many clinicians may feel that ibandronate is best suited for these patients:

- women who feel that even once weekly dosing is too inconvenient, and
- younger postmenopausal women who are not at high or immediate risk for hip or other nonvertebral fractures.

FAST TRACK

In the MOBILE study, the 150-mg monthly dose of ibandronate was superior to daily use in terms of lumbar spine bone density

ADDITIONAL REFERENCES

Chesnut CH III, Skag A, Christiansen C, et al for the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE). Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004;19:1241–1249.

Delmas PD, Recker RR, Chestnut CH III, et al. Daily and intermittent oral ibandronate normalize bone turnover and provide significant reduction in vertebral fracture risk: results from the BONE study. Osteoporos Int. 2004;15:792–798.

Reginster JY, Felsenberg D, Cooper C, et al. A new concept for bisphosphonate therapy: a rationale for the development of monthly oral dosing of ibandronate. Osteoporos Int. 2005 Jun 14; [Epub ahead of print].

CONTINUED

8 years on raloxifene

Martino S, Cauley JA, Barrett-Connor E, et al for the CORE Investigators. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst. 2004;96:1751–1761.

FAST TRACK

Raloxifene has no time limit

- In postmenopausal women at high risk for breast cancer who also need bone pharmacotherapy, raloxifene offers an additional benefit in the breast as well as in the skeleton.

Raloxifene was FDA approved in 1997 for prevention of postmenopausal osteoporosis. This indication was extended to treatment of postmenopausal osteoporosis in 1999. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial of 7,705 women with postmenopausal osteoporosis found that, after 3 years, the women with no previous vertebral fracture had a 30% decrease in vertebral fractures compared to placebo, and there was a 55% decrease in the women with previous vertebral fracture (a higher risk group).

How low can you go?

The MORE trial failed to show a reduction in hip fracture. However, the rate of hip fracture in the placebo group was very low (0.7%) compared to that of placebo groups in an alendronate trial known as FIT I (2.2% placebo group) and the risedronate trial (3.9% placebo group) conducted by McClung and colleagues. This finding underscores the notion that it is difficult to lower risk if a group's risk level is initially low.

Efficacy after 8 years. The Continuing Outcomes Relevant to Evista (CORE) study, which included 5,213 women, extended the MORE trial for 4 years. The primary endpoint was new-onset invasive breast cancer. After 4 years of the original MORE trial, the incidence of invasive breast cancer among patients given raloxifene was reduced 72% compared to that among patients given placebo. At the end of 8 years, the incidence of invasive breast cancer and estrogen-receptor positive breast cancer were reduced by 66% and 76%, respectively, compared with placebo.

A second chance

Unlike tamoxifen (the original selective estrogen receptor modulator [SERM]) whose use in women with breast cancer is limited to 5 years, raloxifene has no time limit. ■

ADDITIONAL REFERENCES

American College of Obstetricians and Gynecologists. Selective estrogen receptor modulators. ACOG Practice Bulletin No. 39. Obstet Gynecol. 2002;100:835:835–844.

Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet. 1996;348:1535–1541.

Delmas PD, Ensrud KE, Adachi JD, et al for the Multiple Outcomes of Raloxifene Evaluation Investigators. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. J Clin Endocrinol Metab. 2002;87:3609–3617.

McClung MR, Geusens P, Miller PD, et al for the Hip Intervention Program Study Group. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med. 2001;344:333–340.

Dr. Goldstein reports that he serves on the gynecology advisory boards for Eli Lilly, Merck, Pfizer, Procter & Gamble, and TAP Pharmaceuticals.