CME CREDIT

Ultrasound and alendronate: New tools for osteoporosis screening and treatment

RICHARD P. TONINO, MD*

Associate Professor of Medicine, University of Vermont College of Medicine; with research interests in the treatment of osteoporosis

ABSTRACT

Office-based physicians can now use ultrasonography of the heel to screen for osteoporosis and estimate the risk of fractures. In treating osteoporosis, alendronate has been shown to increase bone mineral density and to decrease the incidence of fractures.

Soon, we will screen all adults for osteoporosis

TWO RECENT DEVELOPMENTS should revolutionize the diagnosis and management of osteoporosis:

- Ultrasound machines are now available that make it possible to estimate the risk of fractures (although dual-energy x-ray absorptiometry, or DEXA, remains the gold standard).
- Alendronate has been shown to increase bone density and decrease the incidence of fractures.

With these tools in hand, physicians now need to create a systematic process for screening for osteoporosis in their primary care patients, and for treating this common and debilitating disease. I envision that soon we will routinely screen all adult patients for osteoporosis, just as we now do for hypertension and hypercholesterolemia.

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EPIDEMIOLOGY OF OSTEOPOROSIS

Osteoporosis is common, affecting 25 million people in the United States. Four of five persons with osteoporosis are women, and among postmenopausal women, the prevalence may be as high as 50%.[1] A 50-year-old woman faces a lifetime risk of pathologic fracture of approximately 40%.

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Approximately 1.5 million persons per year suffer fractures as a result of osteoporosis, at a cost of nearly $10 billion.[2] More women have osteoporosis-related fractures than have uterine, breast, or ovarian cancer combined.

Too often, osteoporosis is diagnosed only after the patient suffers a fragility fracture. We need to do more to detect and treat it before fractures develop.

ULTRASOUND FOR DETECTING OSTEOPOROSIS

Bone mineral density is reported in several ways: in g/cm^2, in standard deviations above or below the mean value for young adults (a scale called the T score), and in standard deviations above or below the mean for normal subjects matched for age and sex (a scale called the z score). The World Health Organization defines osteoporosis as a T score of –2.5 or lower, and osteopenia as a T score between –1 and –2.5.[3]

Dual-energy x-ray absorptiometry (DEXA) is the most commonly used method for measuring bone mineral density. It is extremely precise, but it has several disadvantages. It is expensive, and therefore probably underused. Some states require that the test be performed by a radiologist or a licensed radiographic technician, increasing the cost. It is inconvenient, because the results are not available immedi-

ately, requiring the patient to return for a follow-up visit.

Advantages of ultrasound

The ultrasound machines now available measure the attenuation and speed of sound passing through the heel bone. This technology obviates the disadvantages of DEXA listed above. The machines are small and portable, and give results within 60 seconds. A nurse or medical assistant can give the test. The machine is relatively inexpensive: approximately $30,000 vs two to three times as much for a DEXA machine. In turn, the test is less expensive.

Another advantage: unlike DEXA, which measures only the density of the bone, ultrasonography also provides information about the architecture of the bone—factors such as trabecular density, spacing, and orientation, which affect the likelihood of fracture.

Is ultrasonography accurate? Critics point out that ultrasound measurements correlate only roughly with DEXA measurements, with an r value of about 0.5.[4] (An r value of 1.0 would indicate a perfect correlation, while a value of 0 would indicate no correlation at all.) The test is done to the calcaneous bone—not the neck of the femur or the vertebrae, which are the most common fracture sites. Moreover, since all the studies of osteoporosis treatment to date have used DEXA measurements, how does one use ultrasonography to evaluate the effect of therapy on bone?

I believe these arguments may be irrelevant. The point of testing is to evaluate the risk of fracture, not the bone mineral density per se, and with either type of measurement the risk of fractures approximately doubles with each standard deviation below the mean.[5,6]

We can combine the ultrasound-derived information with information derived from the patient's history and predict her risk of fracture more accurately. For example, a woman's risk of hip fracture doubles again if her mother ever had a hip fracture, and increases yet again if she herself had a fragility fracture.

ALENDRONATE FOR TREATING OSTEOPOROSIS

Alendronate is a bisphosphonate, a family of molecules with a high affinity for hydroxyapatite crystals in bone. Once they bind to bone, they have a half-life similar to that of calcium: approximately 10 years.

Bisphosphonates inhibit both the bone-resorbing osteoclasts and, to a lesser degree, the bone-depositing osteoblasts. However, the newer bisphosphonates such as alendronate are much more specific in their action on the osteoclasts than are older agents such as etidronate. The net effect is an increase in bone deposition and bone mineral density.

Studies with alendronate

Effects on bone mineral density. In controlled studies in postmenopausal women with osteoporosis,[7,8] alendronate therapy increased bone mineral density by approximately 2% to 9% over 3 years, depending on the site measured. In general, the increases in the lumbar spine were slightly greater than the increases in the hip, which in turn were greater than the increases in total-body measurements.

In contrast, patients receiving placebo lost approximately 1% of their bone density in 3 years, even though all patients received supplemental calcium and vitamin D.

Effects on fracture incidence. In two studies,[8,9] alendronate therapy decreased the incidence of fractures by approximately 50%, with somewhat greater decreases in fractures of the spine and hip than of other bones.

Combine ultrasound information with patient history to estimate fracture risk

Adverse effects of alendronate

Alendronate appears to be safe and well tolerated. Side effects are mainly gastrointestinal and include abdominal pain, dyspepsia, and flatulence.

Esophagitis has been reported in 199 of approximately 470,000 persons taking alendronate worldwide.[10] Persons may be more vulnerable to this effect if they lie down after taking the drug, or take it with less than a full glass of water (see the discussion of dosing, below).

Metabolism of alendronate

Less than 1% of an oral dose of alendronate is absorbed, and the drug is cleared almost entirely by the kidneys. It does not induce the cytochrome P450 system and thus does not potentiate or inhibit the action of other drugs.

Dosage of alendronate

The optimum dosage of alendronate for the treatment of osteoporosis is 10 mg daily.[8,9] To prevent osteoporosis in women with osteopenia, the dosage is 5 mg.[11]

To maximize absorption, patients should take alendronate with a cup of water at least 30 minutes before the first food, medication, or beverage of the day. Taking it with breakfast or within 2 hours afterward reduces absorption by more than 90%. Even taking the drug with black coffee or orange juice reduces absorption by approximately 60%.

Because alendronate can irritate the mucosa of the upper gastrointestinal system, patients should take a full glass of water with the drug, and remain upright afterward.

How long to take alendronate?

Since bone resorption and deposition are strongly linked, we would expect the effectiveness of bisphosphonates to diminish over years of continuous use. In the studies cited above, patients continued to gain bone density throughout the 3 years of the studies, but most of the increase occurred in the first year. A 5-year study showed that there was little additional increase after 3 years.[12] It is important to note, however, that the gains are maintained with continued use.

Black coffee reduces alendronate absorption by about 60%

After patients stop taking alendronate they begin to lose bone mineral density again, but at a rate similar to that in patients who never took alendronate.[13] In contrast, patients who stop taking estrogen or calcitonin experience accelerated bone loss.

These facts suggest that the best strategy would be to take alendronate for several years and then stop or take a low maintenance dose. Another possibility might be to take alendronate only once a week instead of daily. Further research is needed to settle this question.

TWO ALTERNATIVES TO ESTROGEN TO PREVENT OSTEOPOROSIS

Bone loss takes place most rapidly in the first few years after menopause. Estrogen replacement is the current standard for preventing osteoporosis, but many women have contraindications to it, experience unacceptable side effects, or simply do not wish to take it.

Two drugs, alendronate and raloxifene, may be good alternatives to estrogen for preventing bone loss early after menopause, although neither of them alleviates menopausal symptoms such as hot flashes.

Alendronate as early postmenopausal intervention

The EPIC study (Early Postmenopausal Intervention Cohort)[11] enrolled 1,609 women in their early postmenopausal years. Their average age was 53 years, and they were a mean of 6 years postmenopause.

Patients who were willing to receive hormone replacement therapy were randomly assigned to receive either placebo, alendronate 2.5 or 5 mg/day, or an estrogen-progestin combination. Those who did not wish to receive estrogen received either placebo or alendronate.

By 2 years, most of the patients receiving placebo had lost bone mineral density. In contrast, most patients receiving estrogen-progestin gained. Patients receiving alendronate also gained, but not as much as with estrogen-progestin. The average gain in the lumbar spine was 4% with hormone replacement therapy, vs 2.9% with alendronate. The average gain in the total hip was 1.8% with hormone replacement, vs 1.3% with alendronate.

The incidence of side effects was no different with alendronate than with placebo. Since patients received estrogen-progestin "open label," no comparison of estrogen side effects would be valid.

Raloxifene

Raloxifene, a selective estrogen-receptor modulator, may be another good alternative. A recent study showed that raloxifene increases bone mineral density and lowers serum cholesterol and low-density lipoprotein levels without stimulating the endometrium.[14] According to the manufacturer, the effect on bone is less than with estrogen replacement (data on file, Lilly Research Laboratory).

THE IMPORTANCE OF CALCIUM AND VITAMIN D

In the studies described above, all patients received supplemental calcium and vitamin D or dietary counseling about these substances.

In a 3-year study,[15] 26 (13%) of 202 elderly persons receiving placebo suffered a nonvertebral fracture, compared with only 11 (6%) of 187 persons receiving 500 mg of calcium plus 700 IU of vitamin D per day.

Many persons do not ingest enough calcium. The United States Recommended Dietary Allowance (USRDA) is 800 mg/day, but I recommend more: 1,500 mg/day for postmenopausal women, and 1,000 mg/day for premenopausal women and postmenopausal women receiving hormone replacement therapy. In addition, I recommend 800 IU/day of vitamin D. (One cup of milk supplies about 300 mg calcium and 100 IU of vitamin D.)

At a minimum, we should try to make sure that people take in at least 400 mg of calcium per day, because levels less than this lead to accelerated bone loss.

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