Noninvasive Imaging Advances for Osteoporosis

Novel three-dimensional technologies may one day replace dual-energy x-ray absorptiometry.

BY ROBERT FINN
San Francisco Bureau

San Francisco — Investigational bone imaging techniques hold the promise of providing clinically useful information about bone structure in three dimensions unattainable with dual-energy x-ray absorptiometry, Mary L. Bouxsein, Ph.D., said at a meeting on osteoporosis sponsored by the University of California, San Francisco.

While dual-energy x-ray absorptiometry (DXA) measurements show moderate to strong correlations with whole bone strength, the technique cannot distinguish specific attributes of three-dimensional geometry, cortical versus cancellous density, trabecular architecture, or intrinsic properties of the bone matrix.

However, there are some exciting newer techniques, although they are currently in the research phase, said Dr. Bouxsein of Harvard Medical School, Boston.

She highlighted the advantages and limitations of five promising novel imaging techniques:

► **Hip strength analysis (HSA).** This technique uses image data from 2-D DXA to derive 3-D geometry. Developed in the early 1980s, HSA uses data from the attenuation profile of the x-ray beam to calculate such things as cortical thickness and bone strength. But HSA makes several assumptions, most notably that there is constant mineral density in the bone and that the neck and shaft of bones are circular.

"This makes a lot of sense in measurements of long bone, and that was where it was first developed," Dr. Bouxsein said. "Now where I think the challenge comes in … applying this exact same technique to measurement of the femoral neck. … It would be a big challenge to extract properties of the cortex using this direct method."

One attraction of HSA is that it requires no new data collection, since researchers can reanalyze old DXA scans with this new technique. However, there is much more attention currently being focused on techniques that are truly three-dimensional.

► **Quantitative computed tomography (QCT).** With QCT, standard CT images are made with a bone-density "phantom" in the viewing area. This allows a quantitative measure of bone density in the final image and gives a 3-D view of bone geometry as well as an isolated look at the trabecular and cortical compartments.

> **'We need several more years to figure out which one of these [imaging techniques], if any, will make their way into clinical practice.'**

The technique's precision, currently at about 2%-6%, is a bit worse than DXA, Dr. Bouxsein said. The radiation dose is higher than DXA, although still low enough to be acceptable for longitudinal studies.

The resolution is on the order of 300 mcm by 1 mm, somewhat too low to resolve individual trabecular elements, which measure about 100-300 mcm in the adult spine.

Studies have shown that QCT does show age- and treatment-related effects and is useful at both axial and peripheral sites. On the other hand, there are no prospective fracture data (although some are coming), reference data are limited, analysis methods are not yet standardized, and marrow fat can influence QCT measurements, with an increase in marrow fat resulting in an apparent decrease in trabecular bone mineral density (BMD).

► **High-resolution peripheral quantitative CT (pQCT).** This technique has become available within the past 2 years. It uses specialized equipment and can measure the peripheral skeleton, including the distal radius and distal tibia.

It has a voxel size of just 82 mcm^3, allowing visualization of trabecular elements and separation of cortical and trabecular compartments, Dr. Bouxsein pointed out.

The technique's precision is quite good, with short-term reproducibility of 0.7%-1.3% for density and 0.9%-5.1% for microarchitecture. Because it's a peripheral technique, the patient receives a relatively low dose of radiation, and because it uses dedicated equipment, measurements are standardized. Using pQCT, researchers have been able to discriminate among osteopenic women with and without a history of fragility fracture, even when their BMDs are quite similar.

On the other hand, pQCT can't be used to measure central sites, and access is quite limited, with only about 10 machines in the world, including three in the United States. Clinical studies have so far been limited.

► **High-resolution MRI (HR-MRI).** This technique for trabecular bone uses standard clinical scanners and allows physicians to conduct virtual bone biopsies. The technique discriminates patients with a history of fragility fracture from controls, uses nonionizing radiation, and may be useful for monitoring response to treatment.

At the moment, HR-MRI can only be used at peripheral sites, although there is some potential for its use at the hip, Dr. Bouxsein noted.

Its resolution is a bit too low, at just about 100-300 mcm, but that is expected to improve with higher magnetic-field strengths.

Its short-term reproducibility, meanwhile, has been measured at a disappointing 3%-8%. Finally, the HR-MRI technique has been the subject of only limited clinical studies.

► **Finite element analysis (FEA).** Dr. Bouxsein said she was particularly excited about this technique, which is a standard engineering technique that has been used for decades to measure the mechanical properties of airliners and other complex structures. FEA for bone can provide multiple strength metrics.

In measuring bone strength, FEA integrates material and structural information from 3-D QCT to create a computer model of an individual patient's bone. That model is then subjected to virtual stresses and strains.

In vitro, FEA has been shown to predict both femoral and vertebral strength better than BMD measurements alone. But only a small number of clinical studies have been conducted.

The overall state of these promising techniques for noninvasive assessment of bone strength are useful "certainly for clinical research, certainly for clinical trials, [but] certainly not for clinical practice," said Dr. Bouxsein.

"We don't have T scores or an absolute prediction of fracture risk. We don't yet have good evidence that we can use these to monitor therapy. We need several more years to figure out which one of these, if any, will make their way into clinical practice. [But] we've certainly learned a lot about the pathophysiology of this disease," she added. ■

Yearly IV Zoledronic Acid Cuts Fractures, Improves Survival

BY MARY ANN MOON
Contributing Writer

An annual intravenous infusion of zoledronic acid reduced the rate of new clinical fractures and improved survival in patients who had recently undergone surgery for a hip fracture, according to Dr. Kenneth W. Lyles and associates in the HORIZON Recurrent Fracture Trial.

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) study, supported by Novartis, is an international clinical trial that compared the potent bisphosphonate with placebo in 2,127 patients followed for a mean of 2 years, the investigators reported on the New England Journal of Medicine Web site. "No other controlled clinical trial has previously shown efficacy of any osteoporosis medication for reducing the recurrence of fracture in patients who already had a broken hip," Dr. Karim Calis and Dr. Frank Pucino wrote in an editorial accompanying the report.

All subjects sustained a hip fracture after minimal trauma and underwent surgical repair, then received their first intravenous infusion within 90 days. They received daily oral calcium and vitamin D supplements, and were allowed concomitant therapy with nasal calcitonin, selective estrogen receptor modulators, hormone therapy, tibolone, or external hip protectors. A total of 1,065 patients were randomly assigned to IV zoledronic acid and 1,062 to IV placebo once yearly. Mean age was 74 years.

A total of 424 new clinical fractures occurred during follow-up. The rate was 8.6% with zoledronic acid and 13.9% with placebo, for a reduction in relative risk of 35%, said Dr. Lyles, of Duke University Medical Center, Durham, N.C. A total of 242 subjects died. Mortality was 9.6% with zoledronic acid and 13.3% with placebo, for a significant 28% relative risk reduction.

Bone mineral density (BMD) at the hip increased 2.6% at 1 year, 4.7% at 2 years, and 5.5% at 3 years in the zoledronic acid group. In the placebo group it fell 1.0%, 0.7%, and 0.9%, respectively. BMD at the femoral neck increased 0.8%, 2.2%, and 3.6% in the zoledronic acid group. It declined in the placebo group 1.0%, 0.7%, and 0.9%. All differences were significant (N. Engl. J. Med. 2007 Sept. 17 [Epub doi:10.1056/NEJMoa074941]).

Rates of overall adverse events and serious adverse events were similar. There were no differences in frequencies of cardiovascular adverse effects nor in rates of renal toxic effects. There were no cases of osteonecrosis of the jaw, which research suggested might be tied to zoledronic acid. There was no evidence of delayed bone healing, either.

In their comment, Dr. Calis and Dr. Pucino, both of the National Institutes of Health, Bethesda, Md., wrote, "Zoledronic acid appears to offer several advantages over other potential therapies, with one important caveat: Although the risk-benefit pendulum has now swung in favor of treatment, additional long-term safety data are essential," (N. Engl. J. Med. 2007 Sept. 17 [Epub10.10565/N EJMe078192]). Future studies should compare treatment with other therapies and address physical function, quality of life, and cost-effectiveness, they added. ■