

Biomarkers, Architecture Assessment on Horizon

BY KERRI WACHTER
Senior Writer

NEW ORLEANS — Of all the factors that contribute to bone strength, the rate of turnover may be most clinically relevant, David Dempster, Ph.D., said at the annual meeting of the International Society for Clinical Densitometry.

At the same time, several recent advances may soon transform the way bone is assessed.

Bone turnover affects each and every one of the other variables that factor into bone strength, including structural factors and material properties, said Dr. Dempster, professor of clinical pathology at Columbia University, New York.

High bone turnover increases remodeling space, accelerates bone loss, disrupts the trabecular microarchitecture, increases mechanical stress concentration, decreases mineralization density, and increases cortical porosity, each of which can undermine bone strength, Dr. Dempster said.

When osteoclast activity exceeds osteoblast activity, there's a deficit on the surface of the trabeculae and within the cortex. "This may not amount to much in terms of bone mass ... but I think that a small amount of missing bone may be important."

As bone mass declines, there is an exponential increase in fracture risk. "Simply by preventing a small amount of bone loss, you will prevent that patient from going up a steep slope in terms of fracture risk," he said.

Another consequence of high turnover is the increase in the destruction of the trabecular microarchitecture. As bone turnover increases, there is a preferential loss of the horizontal trabeculae known as cross-ties, said Dr. Dempster.

"I'm talking about high turnover in a catabolic sense ... where resorption exceeds formation." This type of turnover occurs shortly after menopause or shortly after the introduction of glucocorti-

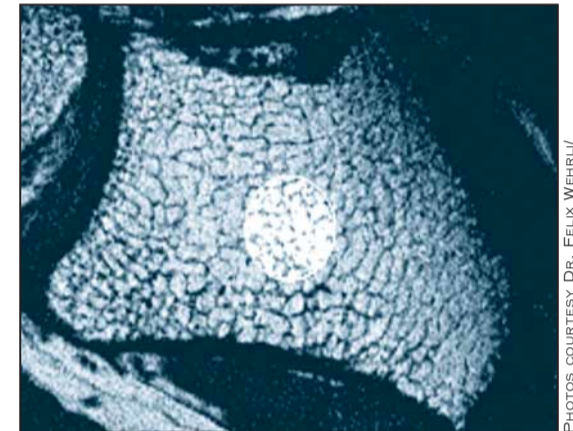
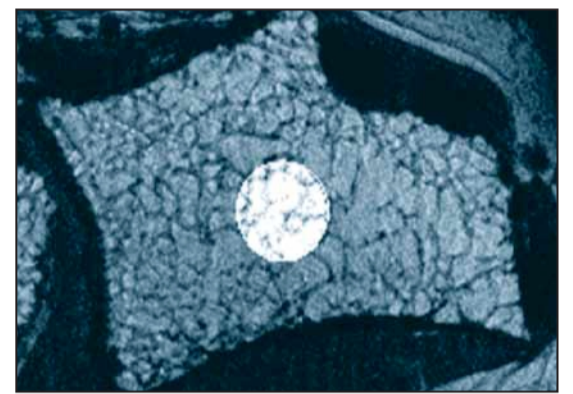
coids, said Dr. Dempster, who is also the director of the Regional Bone Center at the Helen Hayes Hospital in West Haverstraw, N.Y.

After menopause, a confluence of three phenomena can occur: a greater number of osteoclasts gather on the bone surface, osteoclasts become more efficient at breaking bone down, and the plates may become thinner. The result is that instead of sweeping across the trabecular surface—as with normal bone turnover—the osteoclasts tend to penetrate through the trabecular plate, leaving osteoblasts without a template for creating new bone. Supportive horizontal trabecular rods eventually become disconnected.

Mechanical stress concentration is another important element of bone strength. Osteoclast resorption cavities are the mechanical stress points. Without these cavities, intact trabeculae bend in response to stress but don't break. When resorption cavities are present, the same force will cause the trabeculae to break.

With high bone turnover, mineral density declines. While measuring bone mineral density (BMD) captures large-scale information on mineralization density, it doesn't provide information on the local distribution of minerals.

Nor do conventional BMD measures provide information on the collagen-to-mineral ratio. Too much mineral makes bones brittle; too much collagen makes them weak.



Patient A (top) and patient B (bottom) have exactly the same bone density scores. However, axial MRI slices of the distal radius, analyzed for their microarchitecture, reveal that patient A requires aggressive treatment, while patient B does not.

PHOTOS COURTESY DR. FELIX WEHRLI/ UNIVERSITY OF PENNSYLVANIA

So far, markers of bone turnover have been shown to be useful in the research setting, by they aren't ready for clinical use, said Dr. Dempster. Still, once they are ready, "I think that a BMD test coupled with a good measure of bone turnover in an individual patient would give you much more information than you currently have."

Improvements to turnover measurement are imminent, as more of these tests are incorporated into auto-analyzer formats. In addition, progress is being made in defining what the normal premenopausal range is for these markers.

"We [also] have some very good research going on looking at how we can assess microarchitecture noninvasively," he

said. Quantitative CT is starting to be used to assess bone strength in hip structural analysis.

These newer techniques help measure not only BMD but also help assesses the structural geometry of cross sections at specific locations of the hip. The evaluation of bone microarchitecture has benefited from the use of technologies such as peripheral quantitative CT and high-resolution micro MRI.

In the past, bone microarchitecture has been hampered by the need to extract bone samples from volunteers and look at these samples under a powerful microscope. These new technologies give researchers an easier way to study a larger pool of volunteers. ■

Pearls on Low Density in the Young, Vertebral Assessment

BY KERRI WACHTER
Senior Writer

NEW ORLEANS — Bone health experts offered their share of helpful clinical insights at the annual meeting of the International Society for Clinical Densitometry.

Here are some of the highlights:

Low Bone Density in the Young

Low bone density is not uncommon in young adults but—at least in the short term—does not carry with it the same relative risk of fracture as in older individuals unless secondary causes of metabolic bone disease are identified, said Andrew J. Laster, M.D., a rheumatologist practicing in North Carolina.

Secondary causes of low BMD include endocrinopathies (hypercalciuria, hypogonadism, hyperparathyroidism, and Cush-

ing's syndrome), some GI disorders (gastroctomy, inflammatory bowel disease, celiac disease, intestinal bypass surgery, primary biliary cirrhosis, and pancreatic insufficiency), genetic disorders (Ehlers-Danlos syndrome, Marfan syndrome, and homocystinuria), and eating disorders (anorexia nervosa, bulimia nervosa, and female athlete triad).

Assessing Fracture Risk Factors

Before experts declare the benefits of addressing a particular risk factor in an individual patient, they should stop and ask some key questions, advised John Kanis, M.D., director of the World Health Organization's Collaborating Centre for Metabolic Bone Diseases in Sheffield, England.

The questions are: Is the risk factor internationally validated? Is it feasible for a primary care physician to assess the risk factor? Is the risk factor intuitive?

When to Do Vertebral Assessments

Paul Miller, M.D., director of the Colorado Center for Bone Research in Lakewood, recommended performing a vertebral assessment in patients with any of the following:

- ▶ Loss of 1.5 inches or more in height.
- ▶ Back pain in patients coming to your office for osteoporosis assessment.
- ▶ Known vertebral deformities or hip fractures.
- ▶ Kyphosis.
- ▶ Chronic glucocorticoid therapy.
- ▶ Age older than 60 years.

Turnover Markers

There are a number of potential advantages to using bone turnover markers, according to Douglas C. Bauer, M.D., of the University of California, San Francisco.

These measurements provide a more dynamic assessment of skeletal metabo-

lism than BMD. More importantly, bone turnover markers rapidly reflect changes as a result of therapy, providing a better means of assessing treatment efficacy.

The most significant disadvantage to using clinical markers is that there is typically very high day-to-day and even time-of-day variability in the results, Dr. Bauer said.

Timing

For a patient who has been on an antiresorptive therapy and who will be taking teriparatide, there is no need for a break between the two therapies, said John Bilezikian, M.D., professor of medicine and pharmacology at Columbia University, New York.

For patients starting therapy for low BMD, Dr. Bilezikian recommends monotherapy with either an antiresorptive or with parathyroid hormone. ■