Role of Bone Quality in Osteoporosis Gets Clearer

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, Dr. Dempster said.

"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 glucocorticoids, 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.

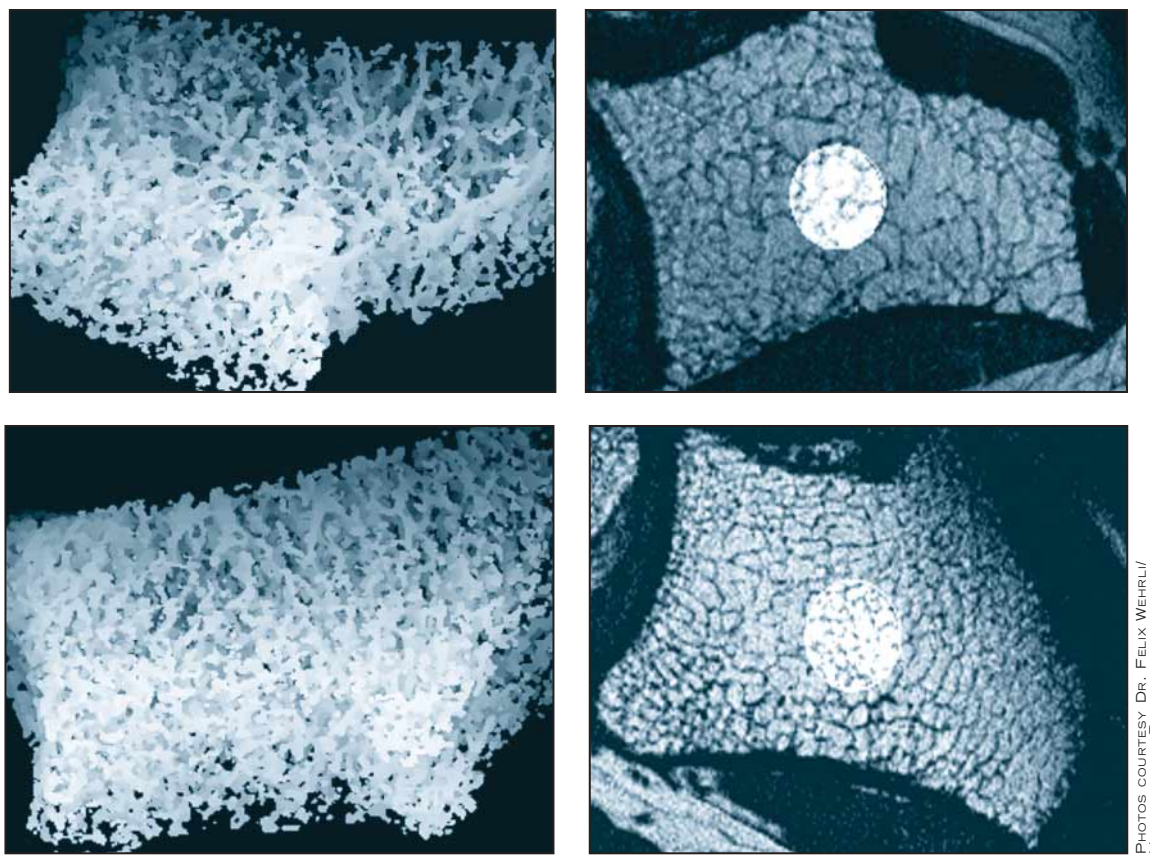
With high bone turnover, mineral density declines. While measuring bone mineral density (BMD) captures large-scale information on mineralization density, it doesn't provide information on the local distribution of minerals. Nor do conventional BMD measures provide information on the collagen-to-mineral ratio. Too much mineral makes bones brittle; too much collagen makes them weak.

So far, markers of bone turnover have been shown to be useful in the research setting, but they aren't ready for clinical use. 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," he said.

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. This technique not only measures BMD but also assesses the structural geometry of cross sections at specific locations of the hip. The evaluation of bone microarchitecture has benefited from the use of new techniques 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. ■



Photos courtesy Dr. Felix Wehrli/University of Pennsylvania

These bone images are from patient A (top two images) and patient B (bottom two images). Both patients have similar bone density scores yet highly different bone structures. These axial slices of the distal radius have been analyzed for their microarchitecture and indicate that patient A requires extensive therapy, but patient B does not.

Compliance Issues Seen With Bisphosphonate Regimens

BY HEIDI SPLETE
Senior Writer

Washington — Postmenopausal women with osteoporosis can reduce their risk for fractures by 26% if they will adhere to their bisphosphonate regimens, Ethel Siris, M.D., reported in a poster presentation at an international symposium sponsored by the National Osteoporosis Foundation.

However, that "if" is a very big one, said Dr. Siris, director of the metabolic bone diseases program at Columbia University Medical Center, New York.

"We assume that there is a relationship between actually taking the drug and having a positive outcome, but it has not been previously demonstrated for bisphosphonate therapy," she said in her oral presentation.

In a retrospective study of 6,285 women, 48% of the participants were compliant in terms of refilling their prescriptions, and 21% were persistent in terms of staying on the medication beyond the 2-year follow-up.

Overall, the relative risk of fracture over a 2-year period was 26% lower among refill-compliant women, compared with noncompliant women (9.4% vs. 12.6%) and 21% lower among treatment persistent women, compared with nonpersistent women (9.1% vs. 11.6%).

More than half (52%) of the study participants were noncomplaint, based on insufficient refills, and 21% discontinued therapy during the 2-year study.

More than half (52%) of the women in the study were noncompliant, based on insufficient refills, and approximately 21% were nonpersistent, defined as having a discontinuation of therapy within the 2-year period.

Data on the pharmaceutical claims of women aged 45 years and older who met the criteria for postmenopausal osteoporosis were taken from the Medstat MarketScan Research Database. The women had received at least one prescription for a bisphosphonate; 85% of them received alendronate (Fosamax) and 15% received risedronate (Actonel).

Although bisphosphonates are a popular choice for fracture risk reduction in osteoporotic women, the drugs' effectiveness depends on compliance over an extended period of time.

And compliance with bisphosphonate treatment is notoriously poor, doctors say. The currently approved daily dose must be taken while the patient is sitting or standing, immediately after waking in the morning. In addition, the patient must allow one hour before eating or drinking anything except water.

"If we actually get people to take these drugs, we might cut as many as 400,000 fractures in a given year," Dr. Siris said. Studies on less frequent dosing regimens, such as the once-monthly regimen for the newly approved ibandronate (Boniva), suggest they are effective and could actually improve compliance.

The need to improve adherence is obvious, given that the U.S. population as a whole averages 1.5 million osteoporotic fractures each year, Dr. Siris noted in her poster.

Dr. Siris serves as a consultant for and has received honoraria from drug manufacturers Eli Lilly & Co., Merck & Co., Sanofi Aventis, Procter and Gamble Pharmaceuticals, and Novartis. ■