

The Role of Bone Mineral Density in the Diagnosis of Osteoporosis

Based on presentations by Robert Marcus, MD; Charles H. Chestnut, III, MD; Harry K. Genant, MD; Kenneth Faulkner, PhD; and Daniel T. Baran, MD

Although measurement of bone mineral density (BMD) is the current standard for diagnosis of osteoporosis, this measurement has

Other aspects of bone quality beyond mass contribute to skeletal fragility.

many limitations, explained Robert Marcus, MD, Professor of Medicine, Stanford University, and Director, Aging Study Unit, Department of Veterans Affairs, Palo Alto, California. However, even with its drawbacks, BMD assessment is the best recourse at present for predicting fracture risk, he added.

Osteoporosis is a condition characterized by global skeletal fragility with decreased bone mass and disturbed microarchitecture of the bones. "It is hard for a clinician to determine if a patient has microarchitectural disruption, so we rely on bone mass measurement. Bone mass measurement is distinct from bone quality. A BMD-based diagnostic criterion may be limited by failing to account for factors collectively referred to as 'bone quality,'" he told listeners.

World Health Organization Diagnostic Criteria

The WHO criteria are based entirely on bone mass. WHO criteria use the bone mass of healthy young women as the norm; a BMD value of 2.5 standard deviations (SD) or below is diagnostic for osteoporosis. Using this value, approxi-

mately 30% of postmenopausal women would be diagnosed with osteoporosis, he explained. The criteria also stipulate a definition of osteopenia for anyone with BMD values of 1 to 2 SD below the norm for healthy young women.

WHO criteria do not take into account ethnicity; however, Asian women and other ethnic groups have lower BMD than Caucasians. Also, these criteria have not been shown to be relevant for men or growing children.

BMD measurements have other limitations. They do not address bone geometry or size. Furthermore, BMD at one skeletal site may not correspond to that of another. Diagnosing a person as normal based on a single site measurement may overlook low BMD at other sites.

Bone Quality

Older people have a substantially higher risk of fracture than young people. This suggests that other aspects of bone quality beyond mass contribute to skeletal fragility, continued Dr. Marcus.

The study of bone quality is still rudimentary, but several factors that determine bone quality have been identified. These include altered bone mineral composition, trabecular disruption, cortical porosity, cement lines, and fatigued accumulation.

Studies of osteoporotic bone specimens reveal a heterogeneity of mineralization. One study found that 25% to 30% of patients with osteoporosis had a substantial degree of undermineralization

of the matrix. Another author suggested that undermineralization confers twice as high a risk of fracture compared to normal mineralization.

As people age, there is an increase in cortical porosity and a disruption of the normal trabecular connectivity. Cortical porosity is difficult to assess, even with a bone biopsy. Normal trabecular bone is a honeycomb of highly connected vertical and horizontal plates. These plates are replaced by shorter and thinner rods in osteoporotic bone, decreasing the load-bearing capacity of the bone. At present, assessment of trabecular connectivity requires taking a 2-dimensional image and creating a 3-dimensional supposition. This is done using a bone biopsy.

Cement lines are the accumulated residua of previous bone remodeling events. They represent the end of the resorption cavity and the reversal line. After many years of bone remodeling, a plethora of cement lines is visible in both cortical and trabecular bone.

Fatigue is a fundamental property of all materials that is a response to repetitive loading of compact bone over time. In bone, this fatigue eventually can lead to a microfracture.

Utility of BMD Measurement

"Despite the limitations of BMD that I have outlined, it has clinical utility," he told the audience. Both cortical porosity and undermineralization are reflected in the BMD measurement, since clinical densitometry depends on the attenuation of photon transmission by bone mineral. Similarly, a serious degree of trabecular thinning and loss of connectivity would be evident in total loss of bone mass. Unremodeled fatigue and cement lines, however, are not encompassed by BMD measurement.

Perhaps newer methodologies, such as ultrasound, will be able to take into account factors related to bone quality. Further refinements are needed before ultrasound is clinically usable for BMD measurements and studies will be needed to validate its use, concluded Dr. Marcus.

BONE MASS MEASUREMENT: TECHNIQUES

Appendicular Bone Mass Measurement

Dual photon x-ray absorptiometry (DEXA) is presently the gold standard for measuring BMD; however, this technology is not widely available in the U.S. Techniques that measure appendicular bone mass (ABM) at the wrist, os calcis, and phalanges, which are more accessible, may be useful for predicting fracture risk in these situations, explained Charles H. Chestnut, III, MD, University of Washington Medical Center, Seattle (Table 1).

Dr. Chestnut posed three important questions about the utility of ABM measurements: "Do they correlate with

Table 1. Available Techniques for ABM

SPA	radionuclides (wrist, os calcis)
SXA	x-ray (wrist, os calcis)
DXA	x-ray (wrist and other sites)
RA	x-ray (phalanges)
pQCT	CT x-ray (wrist)
US (ultrasound)	(os calcis, patella)

bone mass measurements at other sites? Do they have the ability to predict fracture risk? Do they have the ability to monitor therapy?"

Both SPA (single photon absorptiometry) and SXA (single x-ray absorptiometry) measurements of the wrist and os calcis have demonstrated a reasonable correlation with measurements at the spine and hand. A decrease in 1 SD from the norm in healthy young women is associated with an increase in relative risk of fracture.

Monitoring response to therapy using ABM over time is more problematic. "The rates of bone mass change are heterogeneous among skeletal sites. It is not well established that we can monitor treatment response with ABM over time," he commented.

DXA at the wrist appears to have a good correlation with BMD at other sites

and a reasonable ability to predict fracture at other sites. When used to monitor treatment with alendronate, a new bisphosphonate recently approved for the treatment of postmenopausal osteoporosis, spinal bone mass increased 6% to 7% over 2 years, and 8% to 9% over 3 years; however, no change was seen during this time in wrist bone density. "This shows that the changes in response to therapy are not homogeneous at all sites," he said. "The discordance at various skeletal sites is greater in women for the first 5 years after menopause than in older women," he added.

RA (radiographic absorptiometry) at the wrist has a reasonable association with DXA at the spine and femur, he continued. Available published data suggest that RA at the wrist can be used to predict fracture risk. The measurement is fairly easy to obtain and the results are available within 2 to 3 days. The equipment takes up less space than DEXA and the cost of obtaining measurements is much less. "If you don't have access to DXA, then RA is a reasonable alternative," he suggested.

In summary, ABM measurements have acceptable precision and logistics. Radiation exposure with these techniques is minimal. The cost is acceptable, \$100.00 or less for measurement of hand ABM. There is a reasonable agreement between the appendicular and axial sites, and appendicular sites do predict fracture risk. The main drawback of these techniques is their inability to evaluate response to therapy at axial sites, concluded Dr. Chestnut.

MEASUREMENT OF AXIAL BONE MASS BY DEXA

DEXA is the current standard for measurements of axial bone mass (central skeleton, including spine and hip). By virtue of its shortened examination time, greater precision, and improved accuracy, it has replaced DPA (dual photon absorptiometry).

"DEXA is a turn-key operation and it is relatively error-free," noted Harry K.

Genant, MD, University of California, San Francisco.

A major advance in DEXA technology is the ability to measure the anterior/posterior and the posterior/anterior lateral projection. This was not possible with the first generation of DEXA machines, explained Dr. Genant.

"The BMD may be artificially increased in the PA measurement of the lumbar spine, due to the presence of osteophytes, aortic calcifications, and degenerative changes associated with aging. A lateral examination of the lumbar spine makes it possible to evaluate the vertebral body with an almost exclusive measurement of the trabecular bone," he said.

Newer DEXA systems that incorporate the ability to measure the lateral projection have good precision and can be used for preliminary screening, he said, but once fractures occur, conventional radiographs are needed.

Accuracy is enhanced by using volumetric estimates from projectional DEXA measurements. "A larger person will have a larger apparent areal density than a smaller person. This is not actual density," he said. Correcting volumetric assessments reduces dependence on body size and appears to improve diagnostic ability at the spine.

An inherent problem in bone mass measurement is the lack of correlation of BMD at one site versus another. "The 45% error in BMD at one site versus another does not mean that the measurement at one site does not have predictability. We need further work to determine which sites are useful for the decision tree," noted Dr. Genant.

QUANTITATIVE COMPUTED TOMOGRAPHY

Quantitative computed tomography (QCT) provides a volumetric, or 3-dimensional, measure of BMD. "It is the only technique that measures true volumetric density, and it is the most sensitive measurement of trabecular vertebral bone," said Kenneth Faulkner, PhD, Oregon

Osteoporosis Center, Portland, Oregon. Techniques such as DXA and SXA measure a projected density (Table 2).

QCT measures true density in spinal trabecular bone (the bone most responsive to therapy in postmenopausal women) and it is widely available; however, it is not a "turn-key" system, like DEXA, in the sense that it is not designed exclusively for BMD measurements. QCT requires special training and ready access to a scanner (CTs may be in use on emergency patients). Without proper training, the rate of error in interpretation can be high.

"QCT with a commercial CT scanner requires special calibration equipment and procedures which, though simple in concept, must be performed with consistency and attention to detail," explained Dr. Faulkner.

Advances have been made in QCT technology, including improved CT systems, new calibration standards, automated software, error checking, and integrated quality control programs.

A recent study of QCT versus DEXA showed that QCT was the more sensitive method (Jergas et al. *J Bone Min Res* 1995, 10(7):1101-1110). In that trial, 55 women with at least one vertebral fracture were compared to 169 fracture-free controls. "In the right hands, performed properly, QCT was better able to separate the two groups of women," said Dr. Faulkner.

Remaining challenges for QCT include automation procedures for all CT systems, standardization of technical factors, calibration standards, and normative data. "This should be taught as a low-dose technique and requires proper training of the technologist," he said. QCT study of the vertebral spine currently costs between \$150 and \$200, roughly the same as DEXA.

pQCT is a newer technique that allows true density measurement with compact miniaturized equipment at a fraction of the cost of a CT scanner. However, these devices are exclusively designed to scan the forearm and currently cost as much as DXA, which

measures density at multiple sites. Furthermore, the correlation between pQCT and DEXA is not particularly strong. "pQCT is an excellent research tool for small animal models," Dr. Faulkner told the audience.

Currently, DEXA remains the clinical measurement of choice, mostly due to its ability to measure multiple skeletal sites. However, advances in QCT may make this a more attractive technique for the future.

QUANTITATIVE ULTRASOUND

"There are presently 40 million women in the U.S. over age 50, and most of these women do not have access to DEXA. For example, there are only 55

Table 2. Comparison of Techniques for Bone Mass Measurement

Technique	Diagnosis	Monitoring	Versatility	Ease
RA	+	-	-	+
SXA	+	+	-	+
DEXA	+	+	+	+
QCT	+	+	-	-
pQCT	+	+	-	+

Courtesy of Kenneth Faulkner, PhD.

DEXA machines in the state of Massachusetts and 85 in Florida. Low-cost ultrasound (US) will be more accessible for assessment of bone mass," said Daniel T. Baran, MD, University of Massachusetts Medical Center, Worcester, Massachusetts.

Quantitative ultrasound (QUS) provides rapid, safe, radiation-free measurement of broadband ultrasound attenuation (BUA) and velocity of sound (VOS). BUA is thought to reflect density and structure, while VOS is thought to reflect density and elasticity, he said.

"The more complex a structure, the more sound is attenuated. Therefore, normal bone will have greater BUA than osteoporotic bone. Bone with more trabecular disruption will have decreased VOS," elaborated Dr. Baran.

"Some of us believe ultrasound provides more information than BMD—

that it shows something about quality (geometry and structure). QUS also gives some idea about bone volume," he observed.

Five retrospective studies show that QUS predicts fracture risk. Two prospective studies of ultrasound were reported at the American Society for Bone and Mineral Research meeting. The EPIDOS study showed that US predicted the risk of hip fracture as well as densitometry. Another study showed that low BUA values and low BMD were associated with an increased risk of subsequent hip and nonspine fracture. "In this study, US fared slightly worse than densitometry in predicting osteoporotic fracture, but US did predict fracture," he said.

In summary, associating QUS values with fracture is similar in magnitude to associating BMD with fracture. QUS may prove useful as a low-cost, readily available technique to target those women at risk for osteoporotic fracture, concluded Dr. Baran.