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# Current Controversies in Bone Densitometry

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*Editor's note: In this issue of Menopause Management we have invited one of the nation's authorities on bone densitometry to address some of the controversies surrounding the use and interpretation of bone density testing. To this end, Dr. Paul Miller provides his personal perspective about some of these important issues in the article below. Dr. Miller is Founding President of the International Society for Clinical Densitometry. He has been influential in training clinicians in the use and interpretation of bone mineral density testing and in the setting of policies about its use in clinical practice.*

## Introduction

Several basic observations should be emphasized and held as guiding principles in the management of postmenopausal osteoporosis (PMO): The disease should not be accepted as an inevitable process of aging; it is both preventable and treatable; and most postmenopausal women lose bone mass after the menopause, regardless of their calcium and vitamin D intake and their level of physical activity/exercise.

If these three points could be ingrained in the minds of readers of this article, a major intent of this author would be secured. Yet, as a medical community, we are far from grasping these very basic principles. The view of osteoporosis is still largely one of a silent process that does not result in fractures in all women, and perceptions of osteoporosis as an “old woman’s disease” remain. Furthermore, misguided lay advertising implies that calcium and exercise alone are adequate preventive measures, and many

women hold to the “it won’t happen to me” mentality. Further precluding optimal approaches to PMO prevention and treatment are inadequacies in risk factor assessment and bone mineral density (BMD) testing to identify at-risk patients.

BMD measurement has become an important tool in the evaluation of postmenopausal women. In clinical practice BMD measurements are used to assess fracture risk, to identify women with osteoporosis, to make decisions about bone-specific treatments and to monitor response to treatment. But despite an abundance of information about bone density measurements, several uncertainties and controversies exist regarding the use of BMD testing and its interpretation. This article will address some of these issues.

## Indications for BMD Testing in the Postmenopausal Population

Accurate identification of at-risk patients is contingent upon the understanding that risk factors for osteoporotic fracture are not necessarily the same as those for low bone mass. It has, in fact, been repeatedly shown that risk factors for low bone density do not accurately predict bone mass values in individual patients.<sup>1</sup> Risk factors for low bone mass cannot be used to diagnose osteoporosis, but BMD can be used to assess the risk of fracture.<sup>2</sup> The combined use of risk factor assessment and BMD more effectively identifies patients at risk for fracture than does either methodology alone.

Indications for BMD assessment have been put forth by the National Osteoporosis Foundation (NOF).<sup>3</sup> NOF’s recommendation for BMD testing in “post-

menopausal women under the age of 65 years, with 1 or more risk factors” is essentially an endorsement of widespread screening of the early postmenopausal population.

Most postmenopausal women have at least one of the many risk factors for fracture (current smoking, maternal history of hip fracture, any fragility fracture after age 45, weight under 127 pounds, poor visual acuity and/or depth perception, long hip axis length, increased body sway, high bone turnover rate, poor tandem gait, inability to rise from a chair without using hands, etc.). At the menopause more than one-third of postmenopausal women have below-average BMD or *T*-scores<sup>4,5</sup> (the standard deviation [SD] above or below the mean BMD of the young-normal reference population database, the criteria for low bone mass put forth by the World Health Organization [WHO]<sup>4,5</sup>).

Since BMD is normally distributed, measuring it is the only way to identify at-risk women; this is especially important for women who either refuse to take estrogen replacement therapy (ERT) or are debating whether to initiate an ERT regimen. For women already on long-term ERT, the justification for recommending BMD measurement at 65 years of age and older is the lack of prospective evidence of fracture benefit in elderly women on ERT, and the greater than expected prevalence of low bone mass in older women who have been on long-term ERT.<sup>6</sup> This latter observation is most likely related to bone loss pathophysiology, which differs in the early versus the later postmenopausal years. Bone loss related to estro-

gen deficiency and bone loss related to aging are two distinctly different mechanisms. Estrogens—and, possibly, estrogen-like agents—might not prevent bone loss in elderly (over age 65) postmenopausal women.<sup>6,7</sup> Since bone-active agents are available that can reduce fractures in elderly women not taking ERT, identification of at-risk patients on long-term ERT seems reasonable.

In many cases, clinical decisions about the timing of preventive interventions can be facilitated by the use of biochemical bone resorption markers. The postmenopausal patient with elevated markers (1 SD above the upper limit for the premenopausal range) is losing bone more rapidly than the postmenopausal woman with a normal marker of bone resorption. In patients with more rapid losses, interventions to protect skeletal mass can be initiated earlier; this can be done even in early postmenopausal women with normal *T*-scores, since these women might experience lower BMD levels earlier in life than do “slow” losers of bone. In this way, the combined use of BMD measurement and bone resorption biomarker assessment can be complementary.

### BMD Technologies

There are many bone mass measurement devices at the clinician's disposal; these devices can be used to assess BMD or its ultrasound equivalent, and are generally classified as “central” or “peripheral” devices. Central devices include the tabletop, dual-energy, x-ray absorptiometry (DEXA) devices and the quantitative computed tomography (QCT) technologies. Peripheral devices include DEXA technologies that measure wrist, finger or heel BMD, the x-ray-based devices that measure finger and/or metacarpal BMD and the ultrasound devices that measure bone density in the heel and/or tibia. The peripheral devices enable broader access to bone mass measurement at lower costs, and they facilitate the recommended widespread screening of the postmenopausal population versus a case-finding (i.e., selective) strategy for identifying at-risk patients.

How do these devices compare to one another? This question is best answered in the context of the reason for obtaining the BMD measurements. Bone mass is assessed for at least one, and sometimes all, of three reasons: fracture prediction, diagnosis of osteoporosis or osteopenia (based on WHO criteria) and monitoring of the natural biology of a process that affects bone, or of the response to therapeutic interventions.

*Fracture prediction.* Fracture prediction with all of the central and peripheral devices is extremely reliable in the elderly population but not very reliable for women in the early postmenopause, since these younger women fracture so infrequently. In addition, increasing age is a powerful and independent risk factor for fracture; the risk increases greatly at age 65 and older, independent of BMD.<sup>8</sup> In fact, all of the prospective fracture trials completed to date consistently document the powerful relationship between low bone mass and increased fracture risk in study populations with an average age of 65 years or older.<sup>9</sup>

As stated above, advancing age alters bone quality in ways that clinicians cannot yet measure; a 75-year-old woman is more likely to experience a fracture over the next 5 years than is a 55-year-old woman with the same bone density.<sup>8</sup> Clinical decisions and patient counseling in these two age groups can be distinctly different because of these differences in risk. The effect of aging on bone quality might also help to explain the way in which BMD measured at a particular skeletal site helps to predict fracture risk. Measuring BMD at the hip itself might be the best strategy for predicting hip fracture risk, but all of the BMD technologies predict fracture risk at all skeletal sites, including the hip. Why should measuring heel BMD predict vertebral or hip fracture? The answer to this question is most likely related to the bone biology of the elderly; specifically, differences in cancellous versus cortical bone are less apparent once an individual turns 70 but, in younger postmenopausal women, there is more discordance in bone

density across skeletal sites than there is in older women.

*Diagnosis.* Diagnosis of osteoporosis based on BMD criteria was established by a working group of the WHO in 1994;<sup>4,5</sup> a *T*-score of  $\leq -2.5$  was selected as diagnostic of osteoporosis because the percentage of postmenopausal Caucasian women with hip BMD at or below this level (i.e., prevalence) approximated the lifetime risk of hip fracture in the population (16%). In addition, the combined prevalence of women with BMD values  $\leq -2.5$  at three skeletal sites (hip, spine and wrist) also approximated the lifetime risk of fracture at these sites (30–40%).<sup>10</sup>

Providing a “number” for osteoporosis diagnosis before a fracture is sustained is analogous to diagnosing hypertension at some cut-off point before a stroke occurs.<sup>11</sup> This is important since the risk of sustaining a second osteoporotic-related fracture is far greater once an initial fracture has occurred. First fracture prevention is, therefore, a clinical goal, as is prevention of the first stroke or myocardial infarction.

The equation for *T*-score calculation is as follows:

$$\frac{(\text{patient's BMD} - \text{mean BMD of Y-NRP}^*)}{\text{SD of Y-NRP}}$$

\*young-normal reference population

At present, the difficulty with *T*-scores is that measurements at different skeletal sites and with different technologies provide discordant results.<sup>12</sup> *T*-scores are calculated from manufacturer-specific young-normal reference databases, which are inconsistent. Small differences in either the young-normal mean BMD or the young-normal SD can yield substantial differences in a single patient's *T*-scores measured at the same skeletal site but calculated from two different manufacturers' machines.<sup>13</sup>

When a consistent young-normal database is used, *T*-score differences are diminished, even when calculated with different technologies at different skeletal sites. A consistent young-normal ref-

erence population database for incorporation into all FDA-approved BMD devices is a project that this author has been spearheading. The project, which will require at least 2 years to complete, will reduce some of the differences in *T*-scores seen among manufacturers.

*T*-scores also vary from one skeletal site to another because of differences in age-related bone loss or in postmenopausal bone loss at different skeletal sites (e.g., spine BMD declines more rapidly than wrist BMD). Differential rates of bone loss from different skeletal sites, and this aspect of bone biology's contribution to *T*-score discrepancies, cannot be corrected by the use of a consistent young-normal database. Even so, it remains to be seen just how much of the *T*-score discrepancy is reduced by the use of a consistent young-normal database, a project supported by the FDA Regulatory Device Division at the Food and Drug Administration's May 17, 1999, hearing on the *T*-score discrepancy issue. Efforts aimed at reducing inconsistencies in BMD assessments are described in "Reducing Inconsistencies in BMD Evaluation" on page 28.

*Monitoring change/treatment efficacy.* Assuming competent, *in vivo*, quality-controlled precision errors have been calculated, central DEXA or QCT technology is clearly more effective for monitoring BMD changes than is peripheral technology.<sup>13</sup> It is, however, the peripheral skeleton, not the devices (which yield highly reproducible and precise measurements), that fails to reflect serial changes over time in response to osteoporosis treatments, for reasons that remain unclear. With the exception of bone loss that can be measured at the wrist in patients with hyperparathyroidism, at the present time axial BMD measurements are preferred for monitoring. In many cases the use of biochemical resorption markers might provide the clinician with the feedback needed to assess a patient's compliance with medical therapy, or to evaluate a drug's absorption or its biologic effect on bone.

### BMD and Fracture Prevention

The distinction between pharmacologic agents approved for prevention versus treatment of PMO is largely one of the FDA; it was made after publication of the U.S. fluoride data,<sup>14</sup> showing increases in BMD but no fracture reduction. FDA approval for osteoporosis prevention requires maintenance of BMD as the approval endpoint. Although fracture reduction is the ultimate endpoint for any osteoporosis intervention, women in the early menopause fracture so infrequently that many years of longitudinal data and exceptionally large numbers of study subjects would be needed to demonstrate a fracture benefit with respect to early postmenopausal bone loss.

It is, however, intuitive that early prevention strategies should result in a reduction in lifetime fracture risk. Statistical models of lifetime fracture risk exist; these are established by taking the known, current (5-year) fracture risk obtained in many prospective, longitudinal fracture trials (relating low BMD to risk in patients over age 65) and extrapolating back to the probable BMD at the menopause, assuming a 1%/year average rate of bone loss from the menopause on. These lifetime fracture models are probably fairly accurate, since recent longer-term (10-year) trials measuring fracture directly<sup>15</sup> have yielded similar results. Hence, since nearly all women lose BMD after the menopause (unless treated with a protective agent), women entering the menopause with low BMD will have a greater lifetime risk of osteoporotic fracture than will those who enter the menopause with normal/higher BMD values.

Postmenopausal women with low bone mass and additional risk factors for fracture are the best candidates for prevention strategies. In the *Physician's Guide to Prevention and Treatment of Osteoporosis*<sup>3</sup> the NOF recommends that postmenopausal women with *T*-scores  $<-2.0$  be considered for osteoporosis-specific therapies, regardless of risk factors; such preventive therapies are recommended for women with *T*-scores  $<-1.5$  when one or more risk factors are present.

Selection of the  $<-2.0$  "cut-point" was based on the evidence that alendronate, residronate and raloxifene seem to work best to reduce incident vertebral fractures, as well as hip and other nonvertebral fractures in women with *T*-scores at or below this level.<sup>16-19</sup> The treatment threshold based on BMD alone should be considered in women without any prevalent fragility fractures.

In patients with existing fragility fractures, osteoporosis may be diagnosed regardless of BMD (or *T*-score value), assuming other secondary causes of bone fragility have been excluded (cancer, osteomalacia, etc.). Fractures do occur in individuals with normal BMD values; other risk factors, such as high rates of bone turnover, might render a bone susceptible to fracture independent of BMD. Since BMD follows a bell-shaped curve distribution at all ages, a patient can have normal BMD when a fracture is sustained, after having had higher BMD levels in the years preceding the fracture.

Treatment should be initiated in patients with fragility fractures regardless of BMD or *T*-score, since such patients are at a much higher risk for future fractures, regardless of the prevailing BMD levels. In patients with *T*-scores  $\leq -1.5$  at the menopause, risk factors that might justify preventive interventions include a maternal history of hip fracture, current smoking, weight under 127 pounds and a personal history of fracture after the age of 40.

### BMD and Osteoporosis Treatment

FDA approval of an agent for treatment of PMO is contingent upon evidence of fracture benefit, not simply increases in BMD. Bone-active agents that increase BMD are felt to be associated with greater fracture reduction than are agents with minimal effects on BMD, as long as bone quality is not altered; this is plausible since there is a linear relationship between BMD and bone strength. High-dose fluoride, for example, induces abnormal bone quality; therefore, for this agent there is a disconnect between BMD and bone strength<sup>20</sup>

that is not seen with other bone-active agents.

Treatment options include alendronate 10 mg/day, residronate 5 mg/day, raloxifene 60 mg/day, and calcitonin 200 IU/day via nasal spray or injection. No head-to-head, simultaneously randomized, prospective trials comparing these agents with regard to fracture reduction have been conducted. Head-to-head trials have, however, been conducted to compare BMD changes in the postmenopausal population. In a trial comparing alendronate (10 mg/day) to nasal calcitonin (200 IU/day),<sup>21</sup> significantly greater increases in BMD and significantly greater decreases in bone resorption markers were observed with alendronate. No fracture outcome was planned in this analysis.

*BMD changes, fracture risk and treatment efficacy.* How important are BMD increases to fracture risk reduction? This question remains a highly debated one. There is no doubt that there is a linear relationship between BMD and bone strength (60-80% of the variability in bone strength is related to bone mineral content), but the relationship between pharmacologically induced changes in BMD and changes in fracture incidence is not clear.

Some authors have suggested that the relationship between BMD changes and fracture reduction is of little importance,<sup>22</sup> while others have maintained that it is highly important.<sup>23,24</sup> It has also been suggested that since the BMD increases seen during the first year of treatment with alendronate and raloxifene can subsequently decrease/regress to “no change” during the second year of treatment (or vice versa), BMD measurements have little value in monitoring patients on these specific therapies.<sup>22</sup> This latter analysis is, however, limited by the lack of control-group data shown in the same regression; this is important because the real question is whether there is a difference between the treated and untreated patients. For bone density to be used in monitoring treatment, a clear understanding of the precision of the test and how to interpret the results is required. For these, and

other, reasons, the article cited above,<sup>22</sup> in which serial BMD measurement is impugned because of “regression to the mean,” is scientifically flawed.

Regardless of these issues, clinicians should become unsettled when a patient on treatment has a “significant” decline in BMD (when that decline can be verified). Such a decline should prompt a discussion about compliance, adequate drug absorption or the possibility of secondary/underlying conditions that might be precluding a positive response to treatment.

### Summary

Postmenopausal osteoporosis should not be accepted as an inevitable consequence of aging. We now have effective agents to prevent bone loss and to reduce fracture risk in women known to have osteoporosis. Diagnosis of PMO has been improved by BMD technologies, but standardiza-

tion and consistent databases among devices are needed before peripheral devices can be used for diagnosis. Although low bone density is an important determinant of fracture risk, BMD results must be interpreted in the context of other risk factors, such as age and previous fracture history. The BMD response to certain therapies must be interpreted carefully and might be complemented by the use of biomarkers. Despite the uncertainties and controversies that exist about the interpretation of BMD results in some settings, the measurement of bone density is an indispensable tool in the skeletal assessment of postmenopausal women. ■

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### Reducing Inconsistencies in BMD Evaluation

Until there is a permanent solution, such as that described below, the FDA is supporting a project to reduce the differences in osteoporosis diagnoses (based on WHO criteria) seen with different manufacturers' BMD devices and at different skeletal sites. Development of the *T*-score Equivalent Data was spearheaded by a joint committee of the International Society for Clinical Densitometry (ISCD) and the NOF. The project involves equating the *T*-scores obtained with different devices and calculated from manufacturer-specific databases that yield the same 5-year hip fracture risk currently seen with a femoral neck *T*-score of -2.5, calculated from the only consistent database (NHANES III), which exists only for the hip.

Moving away from *T*-scores to an absolute BMD number for either risk assessment or diagnosis of osteoporosis also has challenges; at present, there are insufficient data to make such a move for all of the different BMD devices. Each manufacturer calibrates its devices differently, even for the same skeletal site; therefore, the absolute BMDs in Gm/Cm<sup>2</sup> differ among manufacturers, even at the same site.<sup>25</sup>

Although a standardized BMD value exists for the spine and hip, such a value does not exist for any technology other than DEXA, and there are no data relating the existing standardized BMD to fracture risk prediction. In the proposed standardized database project, it is also planned to measure BMD by all FDA-approved devices in an older population (55-90 years) with and without fractures.<sup>26</sup> By conducting this portion of the project (“Mother and Grandmother of all Databases”), a standardized BMD calculated among all FDA-approved devices will be linked to fracture risk in a consistent population. This will enable an important choice in the osteoporosis field; namely, the clinician could use either the more common *T*-score for diagnosis (from the common young-normal consistent database), or could use a single, standardized BMD value for all the BMD devices when predicting fracture risk.

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- 2001 NAMS/Organon Education Excellence Award—Recognizing a consumer educator among the NAMS membership.
- 2001 NAMS/Protein Technologies International Soy Research Award—Recognizing an individual for his/her body of work that has contributed to increasing the understanding of the role of soy foods in women's health.
- 2001 NAMS/Eli Lilly and Company Award for Innovations in Osteoporosis—Recognizing an individual for his/her body of work relating to the diagnosis, prevention and/or treatment of postmenopausal osteoporosis.
- 2001 NAMS/Eli Lilly and Company SERM Research Award—Recognizing an individual for his/her body of work relating to SERMs for any indication, including osteoporosis.
- 2001 Ortho-McNeil Pharmaceutical Research Award—Recognizing an individual for his/her body of work that increases understanding of issues surrounding the benefit/risk ratio associated with the use of combined estrogen and progestogen therapy (HRT) in peri- and postmenopausal women.
- 2001 NAMS/Wyeth-Ayerst Nurse Practitioner Reporter Program—Providing assistance to 10 outstanding nurse practitioners who are not NAMS members so that they can come to the Annual Meeting and learn more about NAMS and menopause.
- 2002 NAMS/Wyeth-Ayerst Women's Health Research Institute Clinical Research Fellowship Grant—Two \$20,000 ERT/HRT research stipends will be announced in 2001 for research to be conducted in 2002.
- 2002 NAMS/Solvay Pharmaceuticals, Inc. Clinical Research Fellowship Grant—A \$20,000 menopause fellowship will be announced in 2001 for research to be conducted in 2002.

Obtain details from NAMS or log on to the NAMS Web site. Deadlines are June 1 (for award nominations) and June 15 (for research fellowship applications).

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