

## Position Statement

# Dual-Energy X-Ray Absorptiometry Technical Issues: The 2007 ISCD Official Positions

**Christine Simonelli,<sup>\*,1,2,a</sup> Robert A. Adler,<sup>3,b</sup> Glen M. Blake,<sup>4,b</sup> JoAnn P. Caudill,<sup>5,b</sup>  
Aliya Khan,<sup>6,b</sup> Ed Leib,<sup>7,b</sup> Michael Maricic,<sup>8,b</sup> Jerilynn C. Prior,<sup>9,b</sup> Sergio Ragi Eis,<sup>10,b</sup>  
Cliff Rosen,<sup>11,b</sup> and David L. Kendler<sup>12,c</sup>**

<sup>1</sup>HealthEast Osteoporosis Care, St. Paul, MN, USA; <sup>2</sup>University of Minnesota, Minneapolis, MN, USA; <sup>3</sup>Hunter Holmes McGuire VA Medical Center, Richmond VA, USA; <sup>4</sup>Guy's Hospital, London, UK; <sup>5</sup>Erickson Retirement Communities, Catonsville, MD, USA; <sup>6</sup>McMaster University, Oakville, Ontario, Canada; <sup>7</sup>University of Vermont, Burlington, VT, USA; <sup>8</sup>Catalina Pointe Arthritis and Rheumatology Specialists, PC, Tucson, AZ, USA; <sup>9</sup>University of British Columbia, Vancouver, British Columbia, Canada; <sup>10</sup>CEDOES, Vitoria, ES, Brazil; <sup>11</sup>Maine Center For Osteoporosis Research & Education, Bangor, ME, USA; and <sup>12</sup>Prohealth Clinical Research Centre, Vancouver, British Columbia, Canada

## Abstract

At the 2007 Position Development Conference, the Dual-Energy X-ray Absorptiometry Technical Task Force investigated three major areas of bone density testing. Although bone mineral density (BMD) testing in men had previously been reviewed at the 2005 Position Development Conference, we reviewed the most recent data in men to develop appropriate indications for bone density testing in men. We continue to recommend screening at age 70 and discuss the clinical risk factors that may be an appropriate indication for earlier BMD testing.

Menopausal transition (perimenopause) was considered an important time to consider BMD evaluation because bone loss may be significant prior to menopause. However, because fracture risk is inherently low in women of this age without other risk factors, screening BMD testing is not appropriate. We discuss the risk factors that are strong indicators of fracture risk that may be increased during the menopause transition. The presence of these risk factors are appropriate indications for BMD testing with applicability of WHO diagnostic categorization.

The issue of establishing a high threshold for BMD was investigated thoroughly and the current literature was reviewed. Despite the fact there is agreement that all BMD values greater than T-score -1.0 are not normal, it was felt that because of the paucity of sensitivity data and confounding factors such as high body mass index, an upper threshold could not be established or recommended at this time. This was felt to be an important area for further research.

**Key Words:** Dual-energy X-ray absorptiometry; high bone density; male osteoporosis; osteoporosis risk factors; perimenopause.

## Introduction

Three specific areas were identified for the Technical Task Force to review at the 2007 Position Development Conference. These include a review of bone density testing indications in men, women at menopause transition, and the question of unusually high bone mineral density.

Bone density testing in men has been underutilized for a number of reasons, including the uncertainty of the

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\*Address correspondence to: Christine Simonelli, MD, Health-East Osteoporosis Care, 1875 Woodwinds Drive, Suite WL-30, Woodbury, MN 55127, USA. E-mail: [csimonelli@healtheast.org](mailto:csimonelli@healtheast.org)

<sup>a</sup>Task Force Chair.

<sup>b</sup>Task Force Member.

<sup>c</sup>PDC Task Force Liaison.

bone density fracture risk relationship in men. Although the previous Position Development Conference in 2005 (1), addressed the need for bone density testing in men and recommended testing for men at age 70, we propose recommendations for bone density testing in younger men. A significant challenge remains in diagnosing osteoporosis in a younger male and the World Health Organization (WHO) diagnostic criteria cannot be applied in the absence of clinical fragility fracture. We did define specific risk factors in younger men, however, that are appropriate indications for bone density testing, including current cigarette smoking (2), excessive alcohol use (>2 units/day average) (3), prior fracture (4), use of glucocorticoid medication (5), hypogonadism (6–9) (endogenous or androgen deprivation therapy), and vitamin D deficiency.

Women in menopause transition are known to be at high risk for accelerated bone loss (10,11), but generally low absolute risk of fracture. However, there are women in this stage of life who are at unusually high risk for fracture and we propose guidelines to help identify these women and consider them appropriate for bone density testing with dual-energy X-ray absorptiometry (DXA). Hypogonadism remains the most consistent predictor of bone loss although other risk factors are considered important including body weight, exercise habits, and prior fragility fracture. A large prospective Dutch study of women aged 46–54 provides us with important prevalence data (12). As women entered menopause, the prevalence of osteoporosis increased from 4.1% to 12.7%, and osteopenia increased from 27% to 42.8%. Fracture rates remained low, however, and we do not feel screening bone density testing is appropriate at menopause transition. When bone density testing is done, however, because the menopause transition is by definition characterized by hypogonadism, the WHO diagnostic categories for postmenopausal women are applied.

For the first time, the Position Development Conference reviewed the question of establishing a high threshold for ‘normal’ bone density values. There is evidence from the pediatric and adult literature that a number of disease states are associated with unusually high bone density values, and some are not protective to bone and in fact may be osteosclerotic pathology that increases fracture risk (13). Examples include osteopetrosis, Paget’s Disease (14,15), fluoride toxicity, and a variety of genetic disorders. More common, are degenerative changes that spuriously elevate bone density but are not necessarily associated with increased fracture risk (16,17,18). High body mass index is strongly associated with higher than average bone density, and has not been documented to increase fracture risk. The problem with establishing an upper threshold for bone density interpretation is the lack of sensitivity for pathologic states that warrant further evaluation and are associated with increased fracture risk. How many patients would need a ‘workup’ to identify an unusual pathology increasing fracture risk, and what would the ‘workup’ entail? Because of the number of unanswered questions, no consensus could be reached on establishment of an upper limit of ‘normal’ bone density.

## Methodology

The methods used to develop, and grading system applied to the ISCD Official Positions, are presented in the Executive Summary that accompanies this paper. In brief, all positions were rated by the Expert Panel on quality of evidence (good, fair, poor); where Good is evidence that includes results from well-designed, well-conducted studies in representative populations; Fair is evidence sufficient to determine effects on outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; and Poor is evidence that is insufficient to assess the effects on outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or information), strength of the recommendation (A, B, and C where A is a strong recommendation supported by the evidence; B is a recommendation supported by the evidence; and C is a recommendation supported primarily by expert opinion), and applicability (worldwide = W or variable, according to local requirements = L). Necessity was also considered with a response of “necessary” indicating that the indication or procedure is “necessary” due to the health benefits outweighing the risk to such an extent that it must be offered to all patients and the magnitude of the expected benefit is not small.

## What are the Guidelines for BMD in Men?

### ISCD Official Position

- Osteoporosis cannot be diagnosed in men under age 50 on the basis of BMD alone.  
Grade: Fair-B-W-Necessary
- BMD testing in men under age 70 should only be performed in the presence of clinical risk factors for fracture.  
Grade: Fair-B-W-Necessary

### Rationale

The question of appropriate use of T-scores and the age for diagnosis of ‘osteoporosis’ in men has been addressed in two earlier Position Development Conferences held in 2003 (19) and 2005 (1). Based on age-related fracture rates, it was felt that men under age 50 were at sufficiently low risk of osteoporotic fracture that WHO diagnostic classification should not be used. In this population, without identified clinical risk, there is no clear association between low bone mass and risk of fragility fracture. Therefore, the WHO densitometric diagnosis of osteoporosis in such younger men is inappropriate since matching of the frequency of low bone mass to fragility fracture rates in the same population is not possible. In younger men with risk factors, particularly glucocorticoid use or prior fracture, unquantified increased risk is likely. Because the data are insufficient to quantify these risks in younger males, a diagnosis of osteoporosis cannot be made according to WHO diagnostic classification. For men and women over age 50, although absolute fracture rates will differ, the risk gradient (relative risk per standard deviation (SD) decrease in BMD) is similar and therefore the WHO diagnostic classification should apply.

Clinical risk factors (CRFs), in combination with BMD measurement, provide a greater sensitivity and specificity than either alone in predicting risk for fracture in older individuals, and this is true for men as well as women (20). Certain clinical risk factors are important predictors of fracture, and BMD testing will enhance fracture risk prediction. The presence of these risk factors provides an appropriate indication for BMD testing. Some of the clinical risk factors for fracture will not be amenable to pharmacologic therapies, which have been proven effective in patients who have low BMD as a risk for fracture. Therefore, caution must be exercised in using risk-factor based calculations of fracture risk to determine pharmacologic treatment decisions, unless relevant clinical trials are available.

### Discussion

Early traumatic fractures in men have made it difficult to define the true prevalence of fragility fractures, both vertebral and non-vertebral. After age 50, however, vertebral fractures are likely fragility fractures and their incidence in men is about one third to one-half that in women (21). Men have larger bones than women (sexual dimorphism possibly attributable to androgen exposure), affording them a higher apparent areal BMD. The Osteoporosis in Men (MrOs) study of 5995 men over age 65 prospectively analyzed the femoral neck (FN), total femur and spine BMD fracture risk relationship with that of a prospective female database from the Study of Osteoporotic Fractures (SOF) (22). Total femur BMD in men was associated with hip fracture RR/SD of 3.2 (confidence interval [CI], 2.4–4.1). This *sex specific* SD decrease in BMD was a stronger relationship for men than that seen for postmenopausal women in SOF (2.1; CI: 1.8–2.4;  $p < 0.001$  for interaction). Spine BMD in men had a weaker association with risk of hip fracture (RR/SD of 1.5; CI: 1.2–2.0). The association of hip BMD with nonvertebral fracture risk was also stronger for men than for women, regardless of whether a male or female reference was used. This suggests that men may fracture at a higher male reference T-score than women. Also, lower total femur BMD (per 0.1 g/cm<sup>2</sup>) in men was associated with greater hip fracture risk in men (MrOs) than the same association for women in SOF. This prospective study shows significantly greater fracture risk in men compared with an historical cohort of women for a given hip or spine BMD using a sex-specific database.

Whether or not the reported relationship between BMD and fracture risk in men is universal and applicable worldwide is not known (23). Registry studies indicate that fracture rates, particularly hip fracture rates, are significantly different around the world, and with different prevalence data there may be a different measured BMD fracture risk relationship. Due to the poorer quality data on the epidemiology of vertebral fracture, prevalence is much harder to validate. For this reason, current recommendations may only be valid in the developed world.

In the meta-analysis by Kanis et al. a risk assessment tool was developed based on review of nine population-based studies in which BMD and CRF were documented at baseline. Poisson regression models were developed for all fractures

and specifically for hip fractures, testing the model for prediction of fractures with and without hip (FN) BMD. Expressing fracture risk as gradient of risk (GR, risk ratio/SD change in risk score), a risk score was developed for hip fracture and all fractures using CRFs alone, BMD alone, and combined CRFs and BMD. Using nine cohorts from prospective population-based studies performed worldwide, risk factor and BMD data were combined to determine the impact of multiple clinical risk factors with and without BMD information to predict fractures. Risk factors previously identified and included in the analysis were:

- parental history of hip fracture (24)
- glucocorticoid use (5)
- history of prior fragility fracture (4)
- current cigarette smoking (2)
- average alcohol intake in excess of 2 units/day (3)
- rheumatoid arthritis (5)

However, in this meta-analysis of risk factors for osteoporotic fracture, specific analyses of risk factors in men are not presented. Although males represent a significant percentage of the study population, males were not included in the validation cohort. The extent of data examined and the consistency of association of risk factors and fracture risk strongly suggests that risk factors are equally important in men and women. In the Kanis analysis, males and females were pooled recognizing similarities in the data are greater than differences. In this analysis, males were evaluated using male normative databases. The aging male skeleton is micro-architecturally different from the aging female skeleton and this may influence the impact of any particular risk factor on fracture risk.

It is estimated that at least 50% of osteoporosis in males is related to an underlying disorder which may have contributed to failure to achieve an ideal peak bone mass, and/or bone loss. These secondary disorders are similar for men and women. They include primary and secondary hyperparathyroidism, diseases of malabsorption, hypercalciuria, hyperthyroidism, Cushing's disease, chronic lung, liver or kidney disease, rheumatoid arthritis, other immunologic diseases, and hypogonadism, among others. A unique syndrome in men, of low IGF-1 with normal GH, is also described.

The greatest clinically useful risk factors for osteoporosis in men are older age, current cigarette smoking, excessive alcohol use (> 2 units/day average), prior fracture, use of glucocorticoids, and androgen deprivation therapy. These are all considered valid indications for BMD testing in men over age 50. Vitamin D deficiency or hypogonadism would also be indications for BMD testing.

A cutpoint age of 70 has been suggested (previous PDC) for BMD screening, based upon the incidence of osteoporotic fracture after this age. There is, however, no evidence that screening men with BMD testing will reduce fractures. Males at age 70 with a BMD T-score  $-2.5$  have a 10-year fracture probability of approximately 10%, supporting the continued recommendation for BMD testing at this age.

### Additional Questions For Future Research

- What BMD/BMC testing would be most appropriate for men as a predictor of fracture risk?
- Should forearm BMD testing be recommended in all men undergoing BMD testing as a greater predictor of risk?

### How Should We Classify BMD for Women in the Menopausal Transition?

#### ISCD Official Position

- BMD testing in women during the menopausal transition should only be done if there is a clinical risk factor for fracture, such as low body weight, prior fracture, or high risk medication use.  
Grade: Fair-C-W-Necessary
- The WHO diagnostic criteria may be applied to women in the menopausal transition.  
Grade: Fair-B-W-Necessary

#### Rationale

Menopause has been defined as the absence of menses in a woman who is in the context of the end of natural menses. Menopausal transition could refer to women who are close to meeting these criteria, and is the preferred terminology. It is important to have diagnostic categorization for women who have undergone BMD assessment. It is also important to not over-investigate women undergoing a natural transition into menopause. The diagnosis of 'women in menopausal transition' is still an area of controversy and there is no firm consensus in the literature. Consistent in the literature is the onset of irregular menses as a hallmark of menopause transition.

We cannot assume that similar risk factors for bone loss in postmenopausal women or men will be important predictors of bone loss for women in the menopausal transition. A number of risk factors have, however, been investigated as potential risk factors for low bone density in this population. For women in menopause transition specifically, however, there are no clear guidelines for BMD testing. Women typically undergo a rapid phase of bone loss that begins approximately 2 to 3 years before the cessation of menses (menopause transition) and continues up to 5 years postmenopause (10,11,25). Fracture risk is, however, dependent on age, and by definition, women undergoing menopausal transition will be at an age of low baseline fracture risk.

#### Discussion

Gonadal status during the menopause transition has been linked to BMD. This was reported in the Study of Women's Health Across the Nation (SWAN), a multisite, longitudinal, cohort study of the menopausal transition, conducted in community-based groups of women (26); a prospective cohort of 272 untreated pre- and perimenopausal women aged 31–59 (27), a 5-yr prospective study of 292 white women aged 35–50 (28), and a Swedish population of 160 women

prospectively followed through their menopause, with 152 women participating at 12 yr of follow-up (29).

In an effort to estimate the prevalence of osteopenia and osteoporosis in perimenopausal women, and to assess determinants of BMD in a Dutch community population, 5896 white Dutch women, representing 73% of the total number of Dutch women in this age group (aged 46–54 yr), were studied (12). All women were interviewed, and BMD of the lumbar spine was measured by DXA. Osteopenia and osteoporosis were defined according to the criteria proposed by a WHO working group for postmenopausal women. In the population studied the prevalence of osteopenia and osteoporosis was 27.3% and 4.1%, respectively. With progression from premenopause to menopause, the prevalence of osteoporosis increased from 0.4% to 12.7%, and that of osteopenia from 14.5% to 42.8%. An increased risk for low BMD was associated with age, menopausal status, and smoking, while alcohol consumption, high body mass index (BMI), and use of estrogens had a protective effect. A random sample of 940 peri- and postmenopausal women ( $n = 2025$ ) of the Osteoporosis Risk Factor and Prevention cross-sectional, general population survey (OSTPRE) study cohort ( $n = 13,100$ ) in Kuopio, Finland assessed risk factors in perimenopause (30). Trained personnel measured BMD at the lumbar spine (LS) and FN and body weight at baseline in 1989–1991, and at 5-yr follow-up in 1994–1997. Five hundred and forty-seven women had never used hormone therapy (HT) and 393 women used part-time or continuous HT during follow-up of 3.8–7.9 yr (mean 5.8 yr). Of the 172 weight losers, 97 had never used HT while 75 used it during follow-up. According to multiple regression analysis on the total study population ( $n = 940$ ), HT use, years since menopause, and weight increase significantly predicted lower annual bone loss at both the LS and FN ( $p < 0.005$ ).

Lack of exercise and compromised muscle strength have also been carefully studied as potential risk factors for bone loss in the perimenopause. Two studies showing the protective effects of exercise were randomized clinical trials, with no loss of BMD at perimenopause in an exercising group (31) and preserved BMD in an endurance exercise group (32). The OSTPRE did record grip strength as positively associated with BMD (33). These 971 pre- to postmenopausal women from the Kuopio OSTPRE study cohort were measured with central DXA and grip strength with pneumatic squeeze dynamometer at baseline (1989–1991), 5 yr (1994–1997), and 10 yr (1999–2001). Women were divided into two groups according to change in grip strength quartile from baseline to 5-yr follow-up: not improved ( $n = 735$ ), and improved ( $n = 236$ ). In the total population, the greatest bone loss was observed in perimenopausal (beginning of menopause during follow-up,  $n = 311$ ) women [ $p < 0.001$  vs premenopausal women ( $n = 139$ )]. The perimenopausal bone loss rate was significantly lower in women in the improved group in comparison to the not improved group ( $p < 0.01$ ), in contrast to the pre- and postmenopausal groups ( $p > 0.05$ ). In a cross-sectional cohort study, Zhang et al. did demonstrate moderate physical activity positively associated with BMD, but other

studies have been unable to show a significant association between exercise activity and bone loss at menopause transition (34,35). Overall, it is unclear if lack of exercise is an important risk factor for maintenance of BMD during menopause transition. There were no studies specifically looking at vitamin D status or supplementation in the menopause transition, but one 2-yr double-blind placebo-controlled study was performed in early postmenopausal women ( $N = 187$ ,  $> 1$  yr postmenopause, mean age 56 yr), comparing 10,000 IU D2 supplementation plus calcium 1000 mg/day with calcium alone (36). Baseline 25OH vitamin D levels were in the normal range ( $82.6 \pm 27.0$  nmol/l). During the 2-yr study period, there was no significant difference in the change in BMD at proximal forearm, lumbar spine (LS), femoral neck (FN), Ward's triangle, and femoral trochanter, measured at 6-mo intervals. Both groups significantly ( $p < 0.005$ ) gained BMD in Ward's triangle and the femoral trochanter from baseline, but significantly ( $p < 0.005$ ) lost bone in the proximal radius. There was no significant change in the LS or FN BMD. Although smoking is a well-known risk factor for osteoporosis in postmenopausal women (37–40), there is very limited data about the impact of use of tobacco and risk for low bone mass in the perimenopause. A recent meta-analysis, including 29 cross-sectional studies and 19 cohort or case-control studies, confirmed that smoking has no major effect on premenopausal bone density (41). Few studies support an association between markers of bone turnover and low BMD in perimenopause (42,43).

Prior fracture is a well-described important risk factor for osteoporosis, and future fracture and is associated with low BMD in adults (4,44–48). There is less data available for prevalent fracture as a risk factor in perimenopause. A retrospective population-based study assessed whether self-reported former fractures sustained at the ages of 20–34 were associated with subsequent fractures sustained at the ages of 35–57 (49). The 12,162 women in the Kuopio Osteoporosis Study, Finland, who responded to fracture questions via postal enquiry in 1989, formed the study population. They reported 589 former and 2092 subsequent fractures. The hazard ratio (HR), with 95% CI, of a subsequent fracture was 1.9 (1.6–2.3) in women with the history of a former fracture, compared with women without such a history. A former low-energy wrist fracture was related to subsequent low-energy wrist [HR = 3.7 (2.0–6.8)] and high-energy nonwrist [HR = 2.4 (1.3–4.4)] fractures, whereas former high-energy nonwrist fractures were related only to subsequent high-energy nonwrist [HR = 2.8 (1.9–4.1)] but not to low-energy wrist [HR = 0.7 (0.3–1.8)] fractures. The analysis of BMD data from a sub-sample of premenopausal women who underwent DXA during 1989–1991, revealed that those with a wrist fracture due to a fall from no greater than standing height at the age of 20–34 recorded 6.5% lower LS BMD ( $p = 0.140$ ) and 10.5% lower femoral BMD ( $p = 0.026$ ) than women without prior fracture, however the corresponding differences for women with a former non-wrist fracture due to high-energy trauma were -1.8% ( $p = 0.721$ ) and -2.4% ( $p = 0.616$ ), respectively. These results suggest that an early premenopausal, low-energy wrist fracture is an indicator of low-peak BMD,

which predisposes to subsequent fractures in general, but high-energy fractures may indicate other extraskelatal factors that predispose to the same types of subsequent fractures.

Most research trials in younger peri- and postmenopausal women do not have fracture outcome data, and surrogate markers of BMD and biochemical markers of bone turnover are used. This includes trials with estrogen (50), alendronate (51,52), risedronate (53), raloxifene (54), and ibandronate (55). Fracture incidence was recorded in the National Osteoporosis Risk Assessment (NORA) trial in younger postmenopausal women with low peripheral BMD T-scores (heel, forearm, or finger) and they were assessed for the impact of age and BMD on fracture (56). Absolute excess (attributable to low BMD) and unadjusted and adjusted relative risks of fracture were calculated. Absolute risk of fracture increased with age for all fracture sites. The relative risk for any fracture per 1 SD decrease in BMD was similar across age groups from 50 to 99 ( $p > 0.07$ ). From the same cohort, one-year fracture rates were determined in early postmenopausal women (57). Thirty-one percent of women 50–64 yr of age had low bone mass (T-scores  $\leq -1.0$ ). During the first year of follow-up, 904 women 50–64 yr of age reported fractures, including 86 hip fractures, accounting for 37% of fractures and 20% of hip fractures reported in the entire NORA cohort. Relative risk for osteoporotic fracture was 1.5 for each SD decrease in BMD for the younger group of women, similar to the relative risk of fracture in the older postmenopausal women, but absolute fracture rates were different. Among the younger women, the absolute risk of fracture remained low. Individuals with T-scores  $\leq -2.0$  had an excess risk of about 14 (based on 20 vs. 6) fractures per 1000 person-years, compared with women with T-scores  $> 1.0$ . The same difference in T-scores would confer an excess of about one hip fracture per 1000 person-years in the younger women and about six hip fractures per 1000 person-years in the older women. It is estimated that approximately 750 BMD tests would need to be done in women aged 50–59 to prevent one hip or vertebral fracture over a 5-yr period (58). Testing in perimenopause must be considered in light of limited intervention data for women with low BMD until there is good evidence to support the cost effectiveness of routine screening or the efficacy of early initiation of therapeutic agents to prevent fractures later in life.

BMD measurements are currently being used with age and other risk factors, most likely including prior fragility fracture and family history of fracture, to form the absolute global fracture risk model being developed by the WHO. The WHO absolute risk study will link absolute risk for all fractures, calculated from validated population studies representing  $> 90,000$  postmenopausal women. This new model may advocate treatment of women whose lower T-scores or younger age might otherwise not have received treatment (59). Applicability of this new standard to perimenopausal women is unknown.

We have learned from the SWAN (60) and other data reviewed in this report that women in menopausal transition have progressive hypogonadism that is associated with declining BMD. In view of this, we feel that the WHO

diagnostic criteria should be applied to perimenopausal women. Further investigation regarding the relationship of perimenopausal bone density and long-term fracture risk are required, however, to provide more definitive guidance as to recommendations for universal screening bone density testing at this phase of life.

**Additional Questions For Future Research**

- What, if any, bone density screening may be useful in women undergoing menopause transition?
- What diagnostic technologies are most appropriate for use in women in menopause transition?
- Does BMD testing in women undergoing menopause transition with risk factors affect behavior or fracture outcomes?

**How do we Define and Interpret High BMD?**

**ISCD Official Position**

No Official Position is available.

**Rationale**

Since 1998 there has been a consensus that DXA scans should be interpreted using the WHO diagnostic guidelines for postmenopausal women (61). A BMD T-score of  $\leq -2.5$  is interpreted as osteoporosis, a T-score between  $-1$  and  $-2.5$  as osteopenia (or low bone mass), with a T-score  $\geq -1$  being normal. The 2005 ISCD Position Development Statement (62) and the NOF Physician’s Guide to Prevention and Treatment of Osteoporosis (63) are both consistent with this recommendation. As a result of these guidelines, in the United States, any BMD value  $> -1$  has arbitrarily been classified as ‘normal’. Limited data in this area were available for review. Most of the reports concerned associations, and there was a lack of sensitivity analysis defining the pathology associated with an unusually high BMD. As a result, there is no threshold for defining high bone density designated at this time.

**Discussion**

Elevated BMD with various thresholds has historically been termed high bone density, elevated bone density, or ‘osteopetrosis’ (64) by various authors. The Osteoporosis Society of Canada “Evidence-based Guidelines for the Diagnosis and Management of Osteoporosis” recommends that only BMD T-scores of  $-1.0$  to  $+2.5$  be reported as ‘normal’ (65).

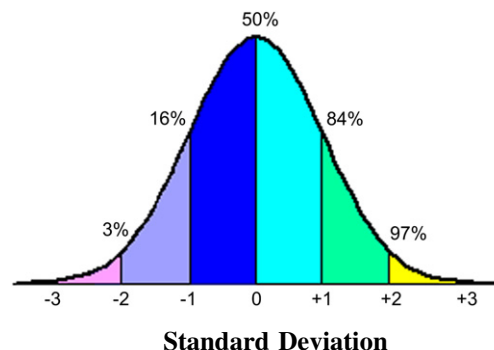
	Age 25	Age 50	Age 65	Age 80
Normal (%)	84	66	40	10
Osteopenia (%)	15	33	40	35
Osteoporosis (%)	1	1	13	27
Severe osteoporosis (%)	1	1	7	27

From Looker et al. 1998 (77).

The percentage of US Caucasian women in WHO categories using femur T-scores is seen in the following table:

The 2005 ISCD Position Development Statement (62) and the NOF Physician’s Guide to Prevention and Treatment of Osteoporosis (63) are both consistent with this recommendation. As a result of these guidelines, in the United States, any BMD value  $> -1$  has arbitrarily been classified as ‘normal’.

T- and Z-scores are based on the statistical unit of the standard deviation. Shown here is the classical bell-shaped (Gaussian) curve with standard deviations below and percent of a population lower than that value shown next to the curve (66).



The Gaussian curve is a symmetrical bell-shaped curve such that 68% of measurements fall within  $\pm 1$  SD, 95% within  $\pm 2$  SD, and 99.7% within  $\pm 3$  SD of the peak value of the curve. The curve is named after the German mathematician Carl Friedrich Gauss (1777–1855) who solved the problem of using astronomical observations of a planet to calculate its orbit round the Sun (67,68). Gauss showed that when data from a large number of observations are combined, each with a small random error, the error in the predicted future position of the planet follows a Gaussian curve. However, unlike the application in astronomy, the use of a Gaussian curve to describe biological data is often only a rough approximation. Biological data can deviate from the ideal curve in two ways: (1) the curve may appear *skewed* rather than symmetrical with the curve dropping away more slowly on one side of the peak than the other and (2) even if the curve is not skewed, the number of data points in the outer wings of the curve may be greater or fewer than the number predicted by a Gaussian curve, a property called *kurtosis*. For Z-score data to be reliably described by a Gaussian curve four things must be true:

1. The mean Z-score should be zero
2. The standard deviation should be 1.0
3. The skewness should be zero
4. The kurtosis should be zero

The bone density is measured in units of  $g/cm^2$ . Bone density naturally decreases with age so the results are also expressed as Z-scores, which are the number of standard deviations below the average for a person of the same age, race, and gender (69). The Z-scores are related to percentiles and both the absolute value (which relates to the strength of the bone), and the relative value (which relates to what is

expected). Standard deviations don't change very much with age. The standard deviation is about 13% to 15% of the average value (coefficient of variation) (66).

The T-score is a linear transformation of the bone density, and depends on the mean and standard deviation at peak bone mass. The original T-scores were calculated only for white women. For white men or black men and women, the T-scores can be calculated using the peak values specific for their race and gender; Hispanic and Asian bone density results are also gender specific. T-scores are calculated by taking the difference between a patient's measured BMD and the mean BMD for healthy young adults, matched for gender and ethnic group, and expressing the difference relative to the young adult population standard deviation (SD) (70).

$$\text{T-score} = \frac{\text{Measured BMD} - \text{Young adult mean BMD}}{\text{Young adult population standard deviation}}$$

The T-score will best identify individuals who have a low BMD, assess fracture risk, and allow for precise monitoring of therapy (71). With aging, the incidence of high T-scores will often increase at the spine, making the lumbar spine a less sensitive measure of potential pathology related to high BMD (17,18). Disease processes that may increase in incidence with aging and increase BMD include degenerative arthritis, compression fractures (72), spondylitis, scoliosis (16), aortic calcifications (73), and surgical changes, among others. Among the committee members there was the impression that using a T-score cut-point of  $\geq +2.5$  SD in the absence of artifacts may be easier for clinicians to understand because it would represent the reverse definition of BMD values from the osteoporotic BMD cut-point of a T-score of  $-2.5$ . However, in fact the question we are really asking is, "How can we identify individuals who have an unusually high BMD who are most likely to have an underlying abnormality?" Once it has been verified that the distribution of Z-score values for a group of subjects follows a Gaussian curve using the four tests described above, the percentage of individuals with high Z-scores greater than a chosen threshold (say  $Z > +2$  or  $+2.5$ ) can be looked up in tables of the Gaussian distribution (Feller W. 1968 An introduction to probability theory and its applications. Vol. 1, 3rd ed. Wiley, New York):

Z-score threshold	% Of healthy subjects
Z > 2.0	2.3
Z > 2.5	0.6
Z > 3.0	0.13
Z > 4.0	0.003

Note that for these predicted percentages to be accurate it is important that the four conditions listed above are met. The Gaussian curve falls off quite sharply in the wings, and real data often have more points in the wings than predicted, e.g., there is significant kurtosis. It is also important that the

values of the mean Z-score and SD are checked. For example, when healthy UK postmenopausal women are evaluated using US reference data, the mean Z-score is  $+0.5$  rather than zero (74). Also, for some reference data (but not NHANES III) the population SD is set unrealistically low leading to a Z-score SD significantly greater than 1.0. Both of these conditions lead to larger numbers of subjects exceeding the Z-score threshold than predicted in Table 1.

By using reference range data it is possible to extend Table 1 and estimate the percentage of individuals with T-scores greater than a chosen threshold (say  $T > +2$  or  $+2.5$ ). This step requires the use of reference range data to calculate the relationship between T-scores and Z-scores. A patient's T- and Z-scores are related by the equation:

$$\text{T-score} = \text{Age Specific Mean T-score} + \text{Z-score}$$

The age specific mean T-score is age dependent and can be calculated from BMD reference data as described by Faulkner et al. (75). Note that this equation assumes that the same population SD is used for calculating T-scores and Z-scores, but the equation can be modified to allow for different SDs if necessary (76). As an example, Table 2 lists the percentage of women with a total hip T-score greater than  $+2.0$  or  $+2.5$  as a function of age, calculated using the NHANES III hip reference range (77).

Estimate of percentages of 'normal' subjects at different ages with NHANES III total hip T-scores greater than  $+2.0$  and  $+2.5$ .

Age (yr)	Mean		Z-score (T = +2.0)	% Subjects (T = +2.5)	Z-score	% Subjects
	Mean BMD	T-score				
20	0.942	0.00	2.00	2.3	2.50	0.6
30	0.939	-0.02	2.02	2.2	2.52	0.6
40	0.922	-0.16	2.16	1.5	2.66	0.4
50	0.886	-0.46	2.46	0.7	2.96	0.15
60	0.827	-0.94	2.94	0.16	3.44	0.03
70	0.759	-1.50	3.50	0.02	4.00	0.003
80	0.691	-2.06	4.06	0.002	4.56	0.0003
85	0.657	-2.34	4.34	0.0007	4.84	0.00007

Although we have the calculated prevalence data, we do not have data to validate the sensitivity and/or specificity of using either the T-score or Z-score in detecting osteosclerotic pathology. It is clear that not all individuals with BMD T-scores  $> -1$  have a normal bone density (78). Most disorders that lead to high BMD are rare, and the average clinician may rarely be confronted with any of these particular diagnoses (5). Furthermore, pathologies which we wish to detect may raise BMD to only a small degree early in their course and would best be detected early by alternative imaging techniques. Osteopetrosis, characterized by generalized high BMD, is a clinical syndrome resulting from the failure of osteoclasts to resorb bone (79). As a consequence, bone modeling and remodeling are impaired. The defect in bone turnover

characteristically results in skeletal fragility despite increased bone mass, and it may also cause hematopoietic insufficiency; disturbed tooth eruption; nerve entrapment syndromes; and growth impairment (80). Other genetic disorders associated with increased bone mass and increased bone fragility include pyknodysostosis. Sclerosteosis (van Beulen's Disease) results in increased bone density with fracture resistance.

A DXA report that a patient has a 'normal' BMD even though the T-score may be greater than +2.5 may be falsely reassuring, although we do not know what percentage of these individuals in fact have a disorder causing high BMD (sensitivity). The prevalence of BMD T-score  $\geq +2.5$  will vary by age, sex, and site measured, with 2.2%–5.8% of women and 4.4%–20% of men having lumbar spine T-scores  $\geq +2.5$ . At the femur sites, however, there are many fewer women (0%–0.3%) and men (0%–1.4%) with T-scores of this value, as noted in a US database of 8000 adults (81). The most compelling argument for setting an upper threshold comes from data that suggest that high BMD associated with underlying pathology may not be protective from fractures and in fact may be associated with a higher than normal incidence of fracture (14). Pathologies resulting in elevated bone density may have other manifestations which require treatment once the patient has been diagnosed. Examples of this would include patients with fluorosis or Paget's disease (14,15). Without an upper limit of normal, there would be no 'trigger' for further investigation and a false reassurance for many patients with significant underlying pathology (13,82).

The most complicating, confounding variable is the influence of weight on BMD. For example, looking at T-scores and Z-scores  $> +2.5$ , 67.1% and 41.9% have BMI  $> 30$  compared with 32.3% and 27.3% having T-score and Z-score values of between  $-1.0$  to  $1.0$  ( $p < 0.001$  and  $p < 0.001$ ), respectively (79).

There is also no consensus on whether it is important to make a distinction between elevated BMD values that are localized and those that are generalized. The pattern of bone density elevation on a DXA scan is important in sorting out the likelihood that there is underlying localized or generalized skeletal pathology of varying degrees of clinical significance. The typical pattern of BMD changes with aging include concomitant progressive degenerative arthritis of the spine creating sclerotic change that is recorded as an elevation in the BMC greater than area, and consequently increased calculated BMD of the spine (83,84). The influence of various forms of spinal degenerative joint disease on BMD was assessed in 299 postmenopausal women (18). Lateral spine radiographs were reviewed for fracture and grade of degenerative joint disease (DJD). When quantitative computed tomography (QCT), lateral-DXA, and posterior/anterior (PA)-DXA measurements were made in the 168 women without fractures, there were no differences in women with and without DJD by QCT or lat-DXA. However, BMD by PA-DXA was significantly higher in women with DJD changes, particularly when osteophytes were present at the vertebral bodies or facet joints. To evaluate the impact of degenerative changes due to osteoarthritis (OA) at the spine, 84 elderly

women were studied with volumetric quantitative computed tomography (vQCT) and central DXA (17). Osteoarthritis was categorized by radiographs, according to severity, as grade 0 or grade 1. Lumbar spine DXA BMD measurements were statistically higher (13%,  $p = 0.02$ ) in the presence of grade 1 OA changes. Femoral trabecular BMD was 13%–15% higher in OA grade 1 subjects than in OA grade 0 subjects by vQCT. Total femur and trochanter ROI were also higher in OA 1 subjects by vQCT. The DXA measurements in the femoral neck and trochanter ROI, however, showed smaller differences (9% and 11%, respectively). This will often, but not always, be evident on visual inspection of the scan images, particularly if there is facet sclerosis, and if spurring is seen on the lateral image. A younger postmenopausal population of 144 women aged 40–84 with a mean age of 63.3 yr referred for routine BMD were evaluated for the presence of osteoarthritis and osteophytosis (83). The finding of degenerative changes in the spine was age dependent, with less than 10% of women affected before age 50, but 40% affected at age 55, and 85% of 70-yr-old women. The magnitude of the increase from osteophytes ranged from 9.5% at L4 to 13.9% at L1. Overall, 59% of the women had some type of degenerative change, either osteophytes, osteochondrosis, vascular calcification, or scoliosis.

Evaluation of individual vertebral BMC and area, and the relationship from one vertebra to the next can be useful. The usual change in BMC and BMD between adjacent vertebrae can be useful and these data were reported in 148 normal women ages 50–60 (85).

Incremental change in BMC and BMD between adjacent vertebrae in 148 normal women ages 50–60 as measured by DXA (86).

Vertebrae	Increase in BMC (g)	% Increase in BMC	Increase in BMD ( $\text{g}/\text{cm}^2$ )	% Increase in BMD
L1-2	2.07	13.7	0.090	7.9
L2-3	2.43	14.8	0.050	4.3
L3-4	1.13	5.0	-0.004	-0.8

Inter-vertebral consistency in bone area (without reduced vertebral height) with high BMC supports a diagnosis of osteoarthritis (87). This should be noted on the bone density report. Plain radiography or other imaging and laboratory diagnostic testing to evaluate an older patient with isolated elevated BMD of the spine may be required for confirmation. If a fracture is suspected clinically because of height loss, back pain or kyphosis, or there is evidence of reduced height of one or more vertebrae relative to adjacent vertebrae, further evaluation by VFA with DXA or plain radiography is recommended (88). In the clinical setting of vertebral fracture with back pain, further laboratory testing may be indicated to exclude underlying secondary cause of osteoporosis such as multiple myeloma (89). In most such instances, other than the compressed vertebra, the bone density would not be elevated. In the setting of spine artifact precluding evaluation of at least

two vertebral levels, diagnostic classification will be made on the total proximal femur, femoral neck, or one-third radius site, whichever is lowest (62). Degenerative arthritis changes do not typically cause BMD elevation at the forearm site (17).

Osteoarthritis can also influence the BMD at the hip. In a larger study of 4090 women studied with radiographs for hip osteoarthritis, a subset of 1225 women also had spine radiographs and DXA (90). An osteoarthritis grading scale for the severity of osteoarthritic changes at the hip ranged from 0 to 4, with 0 indicating the absence of arthritis; grade 2 or higher representing the presence of osteophytes or joint space narrowing; and grades 3 and 4 being consistent with moderate or severe disease. Women with at least grade 3 severity in either hip had a higher BMD at all sites including PA spine, femur, and radius. After adjusting for age, the increase in BMD was approximately 8%–10% at the femoral neck and lumbar spine, and 3%–5% at the distal radius and trochanter. Women with grade 2 osteoarthritis also had increases in BMD at all sites but the increases were in the range of 2%–4%. The increased BMD at the hip was corrected for by the fact that there is some inability to adequately rotate the femur internally due to arthritis (91), but the increase in BMD persisted. Similarly, the lumbar spine BMD may also be influenced by osteophytes and sclerosis of the spine and after adjusting for this, there was still a significant increase in BMD in grades 3 and 4 osteoarthritis.

Aortic calcification increases in prevalence with advancing age, so that 60% of women in their 60s and 70% of women in their 70s have visible aortic calcification detected radiographically (92). In 200 women, linear calcifications and calcified plaques were graded 0 (no calcification), grade 1 minimal and grade 2 severe calcification. The percentage of women with severe aortic calcification was low at any age and was found in only 30% in women age 80. There was no significant increase in BMD in the presence of aortic calcification. A number of studies have looked at the potential influence of aortic calcification on PA and lateral lumbar spine DXA, and aortic calcification was not easily seen on most PA lumbar spine studies. It was, however, easily identified on VFA imaging. The influence on BMD, even in women age 80, was not statistically significant and this has been shown in a number of studies in women (92,93) and in men (94,95).

Other focal BMD increases may be important to note. Paget's disease of bone may be either monostotic or polyostotic. When within the DXA region of interest, Pagetic bone may increase BMC to a greater degree than bone area resulting in increased BMD. Pagetic lesions may be confirmed by plain film radiography, which may show regional sclerotic change with or without bony expansion and osteolytic changes (96). Pagetic bone demonstrates increased isotope uptake on radionuclide bone scan. Since biochemical markers of bone turnover are increased, serum alkaline phosphatase or bone specific alkaline phosphatase can be used to monitor disease activity in Paget's disease. Involved trabecular Pagetic bone BMD has been reported to be increased by 25%, with involved cortical BMD 35% higher than non-Pagetic bone (97). The clinical context of a patient with regional BMD elevation as well as the DXA image appearance of bony enlargement may suggest Paget's disease of bone.

Genetic aberrations will be associated with generalized elevations in BMD, including LRP5 mutation (98), mutation of cathepsin K (99), or other genetic mutations causing heritable osteosclerotic disorders. A case of a 34-yr-old African-American male with multiple fragility fractures and high BMD was initially thought to be Paget's Disease with osteosclerosis on plain radiography and diffuse symmetric osteosclerosis of both the axial and the appendicular skeleton (100). The eventual diagnosis was osteopetrosis type 2, an example of a genetic disorder first diagnosed in adulthood.

Intoxication with fluoride can be associated with an elevation of central BMD as reported by Kurland et al. (101). Radiographic osteosclerosis is reported in a case of a man with BMD Z-scores of +14 at the lumbar spine, +6.6 at the femur, and -0.06 at the radius. The preferentially less affected site of the cortical radius is consistent with the histopathologic pattern in fluorosis showing increased trabecular bone volume (102). Endemic water borne fluorosis, a public health problem in southern Turkey is estimated to be responsible for one third of the osteosclerosis found in that region (103). On retrospective review of 1500 patient BMD scans of the lumbar spine and femoral neck, 69 patients were found to have BMD T-scores  $\geq +2.0$ . Of these, 34 underwent repeat bone density evaluation and were investigated for fluorosis and other etiologic causes of osteosclerosis. Five patients (34.7%) had signs of fluorosis. Patients with short-bowel syndrome on long-term (> 1 yr) home parenteral nutrition (HPN) had fluoride levels, measured by using a fluoride-sensitive electrode, and underwent BMD testing with DXA (104). They had variable amounts of fluoride in their HPN and other beverages. Of 120 fluoride dosages (2–6 mg/patient), 102 were above the upper normal limit (1.58 micromol/l) at the laboratory. Mean ( $\pm$ SD) daily fluoride supply was  $8.03 \pm 7.71$  mg (US adequate intake: 3.1 mg/d for women and 3.8 for men; tolerable upper normal limit: 10 mg/d); intravenous fluoride varied from 0.06 to 1.45 mg, and oral fluoride varied from 0.09 to 27.8 mg. Serum fluoride concentrations were correlated with creatinine clearance and fluoride supply. After adjustment for sex and the duration of HPN, only the effect of serum fluoride on spinal BMD was significant. Two patients had symptoms of fluorosis, e.g., calcaneum fissures, interosseous calcifications, or femoral neck osteoporosis.

Generalized high skeletal BMD should be interpreted in the clinical context of the patient, and with great care taken to ensure that no pathological condition exists. Specific diagnoses are not evident by high bone density alone. In a postmenopausal woman of any age, generalized BMD elevation may be viewed as a potential marker of lifetime estrogen exposure, and has reportedly been associated with more advanced breast cancer in elderly women. The relatively exhaustive list noted in the Whyte paper and other text references can be used as a review for the interpreting clinician (15,105,106).

There are no specific data about the true incidence of underlying pathology in the context of an elevated BMD T-score. A number of relatively rare disorders are associated with a high BMD in adults, and the clinical context will be

important in determining how actively any of these are investigated. Osteopetrosis (marble bone disease), is a genetic condition characterized by a high bone density (107,108). Over 300 cases have been reported in the international literature. The autosomal dominant adult (benign) type that may be detected by DXA is asymptomatic (109). Generalized symmetric increase in bone mass is the principal finding, and on lateral view vertebrae may show a 'bone-in bone' or 'rugger jersey' appearance (110). The childhood (malignant) autosomal recessive type, is most often fatal by early childhood (111). There is also a fourth clinical type inherited as an autosomal recessive trait with associated renal tubular acidosis and cerebral calcification that is actually a carbonic anhydrase II deficiency (112). It is recommended that we avoid the term 'osteopetrosis' as a generic term for osteosclerosis since it refers specifically to conditions with known genetic etiologies (113). Although rare, the commonest disorders associated with a high BMD include various dysplasias and dysostoses that will most likely be diagnosed in childhood, a variety of metabolic disorders including fluorosis, hypervitaminosis A or D, hypoparathyroidism, pseudohypoparathyroidism, mastocytosis, and heavy metal poisoning and numerous other disorders, such as diffuse idiopathic skeletal hyperostosis (DISH), bone marrow dyscrasias, osteonecrosis, sarcoidosis, and skeletal metastases (15). Ten cases have been reported of a syndrome of osteosclerosis in intravenous drug abusers exposed to hepatitis C virus through blood transfusion (114). BMD is reportedly 200%–300% above the age and sex-matched mean (Z-score). Bone marrow dyscrasias typically associated with osteoporosis, such as multiple myeloma, can also present with widespread osteosclerosis (81). Mastocytosis and myelosclerosis can also be associated with high BMD (113). Genetic studies based on cohorts with extreme bone phenotypes have shown that the LRP5 gene is an important genetic modulator of BMD (115). To study the influence of LRP5 polymorphisms on normal variation in BMD, data from a cross-sectional study of individuals with either osteoporotic BMD ( $n = 152$ ) or BMD T-score  $\geq +2.5$  ( $n = 160$ ) were evaluated, and certain genetic haplotypes were found to be more frequently associated with high BMD than other polymorphisms.

A major point of discussion lies with the increasing body of data which shows that high BMD may be reflective of lifetime estrogen exposure in a woman, or lifetime androgen exposure in a woman or man (116,117). When the descriptive, cross-sectional Postmenopausal Estrogen/Progestin Interventions Study (PEPI) of early postmenopausal women was revisited, a positive association between women with a mammographic breast density and bone mineral density was observed (118). This was confounded by current or recent postmenopausal hormone therapy use. The case-controlled study by Ganry et al., in 2001, looked at lumbar spine, femoral neck, trochanter, and Ward's triangle BMD in 126 women, and reported that BMD was significantly higher in breast cancer patients at all sites (119). After adjusting for potential confounding factors, the relative risk of breast cancer in the highest quartile of BMD compared to the lowest

quartile ranged from 2.5 to 4.8 for the various sites measured. They proposed that it was the cumulative exposure to estrogen that posed the increased risk for breast cancer and protection against osteoporosis. In the prospective Study of Osteoporotic Fractures (120), 8905 women of at least 65 years of age without breast cancer were followed a mean of 6.5 years. During 57,516 person-years of follow-up, 315 women developed breast cancer. Multivariate analysis adjusted for other covariates revealed that the risk of breast cancer for women in the highest quartile of BMD of the wrist, forearm and heel using single-photon absorptiometry, was 2.7 (95% CI: 1.4–5.3) compared with women in the lowest quartile. The magnitude of the increased risk was greater for more advanced tumors. The Dubbo Osteoporosis Epidemiology Study (121) investigated the association between BMD and breast cancer in a nested case-control study involving 30 breast cancer cases and 120 controls with a mean age of 68. Using DXA measurements at the lumbar spine and femoral neck they reported that among breast cancer cases 20% had LS BMD values greater than 1.2 g/cm<sup>2</sup>, or T-score  $> +2.5$  compared with less than 1% of the controls. After adjusting for lifetime ovulation and body mass index, they calculated that each 0.1 g/cm<sup>2</sup> increase in LS and FN BMD was associated with a 2.1-fold (95% CI: 1.3–3.4) and 1.5-fold (95% CI: 1.0–2.4) respectively, higher risk of breast cancer. They estimated that estrogen therapy in osteoporotic women, even if increasing risk of breast cancer, would not elevate their risk to the level experienced by their non-osteoporotic counterparts.

Somewhat contradictory data come from the cross-sectional study of 15,254 women, and a nested, case-controlled study of 208 women with breast cancer and 436 control subjects (122). All subjects had undergone both mammography with breast density quantitation using the American College of Radiology Breast Imaging Reporting and Data system (BI-RADS) and percentage mammographic breast density was quantitated. Using logistic regression there was no correlation between hip or spine BMD and BI-RADS (correlation coefficient  $-0.2$  and  $-0.01$ , respectively) and bone density testing. Women with the highest sextile of breast density, however, had a threefold increased risk of breast cancer compared with women in the lowest sextile (odds ratio = 2.7, 95% CI: 1.4–5.4). They concluded that BMD, although a possible marker of lifetime exposure to estrogen was not associated with breast cancer. With this contradictory data in hand we must exercise caution in suggesting that a woman with a high BMD may be at increased risk of breast cancer.

Because of the association of breast cancer and high BMD, Vandevord et al. hypothesized a differential effect on hormone responsive genes when complexed with hormones (123). They looked at estrogen receptor-alpha (ER) and vitamin D receptor (VDR) polymorphisms because of their known association with BMD. They examined the polymorphisms for an association with increased breast cancer risk in a case-control study. Genotypes and BMD were obtained from 412 women (220 cases and 192 controls, equally distributed among white women and African-American women).

They found no evidence for an association between either the ER or the VDR genotypes and breast cancer risk. There was also no difference in the risk of breast cancer by genotypes after adjusting for ethnicity. Their data suggests that the polymorphisms tested had no effect on risk of breast cancer, and no evidence to support the hypothesis that breast cancer cases and controls would have a different distribution of ER and VDR genotypes.

High bone density is also reported in hyperandrogenic women. Simberg prospectively studied 20 hirsute patients and 19 age-matched controls who underwent GnRH implantation. The data (baseline, and after GnRH implant for 9 months, with half the patients randomized to estrogen/progestin therapy) (124), showed that ovarian androgen excess was associated high BMD that was lost during GnRH agonist therapy and regained with estrogen/progestin therapy.

Since the true incidence of an underlying abnormality in the context of a 'high' BMD is not known, caution should be used in offering specific advice about possible diagnosis. We are of the opinion that a possible association between high BMD, lifetime estrogen exposure, and breast cancer risk might be reasonable to include in reports if clinically appropriate.

### Additional Questions For Future Research

- Is it important to define an upper limit of normal BMD?
- What is the sensitivity of a particular unusually high BMD for detecting pathology that may increase fracture risk?
- What is the incidence of 'high BMD' associated pathological states that increase fracture risk?
- How can we best control for high BMI that may be protective against fracture risk and high BMD associated pathologic states?

### Summary

Bone density assessment in men age 70 and older remains an important aspect of an overall osteoporosis risk assessment. In men younger than 70 yr, BMD testing is appropriate in the presence of clinical risk factors for fracture. Specific clinical risk factors in men, independent of bone density and in addition to older age, include current cigarette smoking; excessive alcohol use, endogenous hypogonadism and that associated with androgen deprivation therapy, prior fracture, glucocorticoid use, and vitamin D deficiency.

Women in menopause transition are, by definition, hypogonadal and have an accelerated phase of bone loss. During the menopause transition, BMD testing is only warranted when significant clinical risk factors for fracture are present, such as low body weight, prior fracture and high risk medication use. Although data are limited, the Expert Panel believe the WHO diagnostic categories may be applied to women in menopause transition.

Regarding the issue of unusually high BMD, there were insufficient sensitivity data to adequately interpret the probability of an individual with a BMD above any particular cutpoint

as having osteosclerotic pathology, or being at increased fracture risk. Certain diseases are associated with higher than usual BMD values, such as T-scores > +2.5. However, individuals with high body mass index are over-represented in the same high bone density cohort. Because of insufficient available data, the PDC Expert Panel was unable to accept any Official Positions for an upper threshold for BMD. An important association of high BMD values and breast cancer in women remains an intriguing area, and knowledge that this data is important for clinicians.

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