Position Statement

Application of the 1994 WHO Classification to Populations Other Than Postmenopausal Caucasian Women: The 2005 ISCD Official Positions

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Abstract

In 2003, the International Society for Clinical Densitometry (ISCD) developed Official Positions regarding the applicability of the World Health Organization (WHO) classification of bone mineral density to populations other than postmenopausal women. However, these prior Official Positions do not fully address bone mineral density reporting in females prior to menopause, men, and non-whites. During the 2005 ISCD Position Development Conference, members of the ISCD Expert Panel in conjunction with the ISCD Scientific Advisory Committee re-addressed these topics and, based upon stringent reviews of best available data, developed ISCD Official Positions that provide greater specificity and clarification with respect to the following: (1) the utility of the term ‘osteopenia’; (2) utilization of T- and Z-scores for bone mineral density reporting; (3) when to apply the WHO densitometric classification; and (4) which normative database(s) should be used for non-white individuals. Briefly, the term ‘osteopenia’ is retained, but ‘low bone mass’ or ‘low bone density’ is preferred. Z-scores, not T-scores, are preferred in females prior to menopause and males under age 50. In these individuals, a Z-score of \(-2.0\) or lower is defined as “below the expected range for age” and a Z-score above \(-2.0\) is “within the expected range for age.” T-scores are preferred and the WHO classification is applicable for postmenopausal women and men age 50 and older. These Official Positions, rationale and evidence are discussed in the following report.

Key Words: Densitometry; osteoporosis; official positions; dual-energy X-ray absorptiometry; DXA.

Introduction

The ability to easily assess bone mineral density (BMD) revolutionized the clinical approach to osteoporosis. This was recognized in the World Health Organization (WHO) definition for osteoporosis as “a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures” (1). Although BMD is recognized as a continuous risk factor for fracture (i.e., no fracture threshold exists), operational ranges for the T-score were proposed (Table 1) for epidemiologic purposes. These criteria have subsequently been applied to assessment of fracture risk, diagnostic classification, and treatment initiation in individuals. The WHO Technical Report intended these categories to be applied only to postmenopausal white (Caucasian) women. This has created uncertainty in diagnosing osteoporosis in other groups such as males, females prior to menopause, and non-whites, who together vastly outnumber postmenopausal white women. The general acceptance of the WHO diagnostic criteria was a sentinel event in the worldwide recognition of osteoporosis as a major public health concern. The International Society for Clinical Densitometry (ISCD) has addressed the limitations of the WHO
I. Use of the Term Osteopenia: Should it Remain in the Densitometry Lexicon?

**ISCD Official Position**

- The term “osteopenia” is retained, but “low bone mass” or “low bone density” is preferred.

**Rationale**

The original purpose of the WHO classification was to provide a framework to allow collection of epidemiological data (1). If the WHO classification was used only as intended, no individual would be diagnosed with ‘osteopenia’ because the label would only be applied to groups of people. Although it was not intended that the WHO classification be applied to individual patients, it works well to define ‘normal’ (T-score = –1.0 and above) and ‘osteoporosis’ (T-score = –2.5 and below). Several large studies have shown a high risk of fracture in patients who have T-scores of –2.5 and below, and a significant reduction in fracture risk with treatment, making this threshold an ‘evidence-based’ criterion for the diagnosis of osteoporosis and for the initiation of treatment.

**Discussion**

Fracture risk is continuous; there is no “fracture threshold” (7). Although it is sometimes useful to think categorically when dealing with a continuous variable, the category of “osteopenia” creates problems in at least four ways. Firstly, subjects in the upper part of this range could be perfectly normal depending on their age. Applying a medical label such as “osteopenia” to a healthy young person can create considerable anxiety that may last lifelong. Secondly, subjects in the upper part of this range are almost as likely to fracture as patients on the lower side of the arbitrary cut point (potentially more likely to fracture, depending on other risk factors for fracture). Apparently healthy patients in the upper part of this range should be candidates for pharmacologic intervention, depending on how low their BMD is and the presence of other risk factors (8). Thirdly, confusion has arisen due to the word “osteopenia” being commonly used by radiologists as a qualitative term to describe the radiographic appearance of bones, and not as a quantitative term as used by bone densitometrists. Finally, patients confuse the term “osteopenia” with “osteoporosis” and often consider that the latter is an equally serious medical disorder requiring treatment. For these reasons, the term “osteopenia” is best avoided. The descriptive term “low bone mass” or “low bone density” is preferred for people with T-scores between –1 and –2.5. This terminology is adopted throughout the remainder of this document.

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**Table 1**

<table>
<thead>
<tr>
<th>Category</th>
<th>T-score</th>
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<tbody>
<tr>
<td>Normal</td>
<td>–1.0 or greater</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Between −1.0 and –2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>–2.5 or less</td>
</tr>
<tr>
<td>Severe or established osteoporosis</td>
<td>–2.5 or less</td>
</tr>
</tbody>
</table>

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*See reference (1).

Units are standard deviations above (positive) or below (negative) the young adult mean value.
Often ignored is the WHO category of ‘severe’ or ‘established’ osteoporosis, meant to apply to patients who have already fractured and have a T-score of −2.5 or less. Although a fragility fracture, particularly a vertebral fracture, is a strong predictor of future fracture, this is true whether the T-score is −2.6 or −2.4. In fact, there is an apparent contradiction: a larger number of patients who have fragility fractures have T-scores above −2.5 (9). Although patients with a T-score consistent with osteoporosis are at higher risk for fractures than those with low bone mass, there are so many more patients with low bone mass that the number of women with fractures in this category is higher. It is possible that some clinicians would not diagnose osteoporosis in a patient with a fragility fracture because the T-score was above 2.5. A patient with low bone mass and fragility fracture may be more likely to fracture in the future than a patient with WHO-defined osteoporosis but without a fragility fracture (10). Patients with a fragility fracture warrant a clinical diagnosis of osteoporosis, have a high risk of future fracture, and should be treated accordingly. Apparently healthy subjects in the upper range of “low bone mass” should be reassured and monitored periodically. Apparently healthy subjects in the lower range of “low bone mass” deserve consideration of pharmacologic intervention. In brief, people with low bone mass or density are not necessarily at high fracture risk and require an individualized approach that considers the importance of other risk factors, most importantly age and prevalent fractures.

II. BMD Reporting

ISCD Official Positions

In Females Prior to Menopause and in Males Younger Than Age 50

- Z-scores, not T-scores, are preferred. This is particularly important in children.
  
  Grade: Poor-C-1

- A Z-score of −2.0 or lower is defined as “below the expected range for age” and a Z-score above −2.0 is “within the expected range for age.”

  Grade: Poor-C-1

In Postmenopausal Women and in Men Age 50 and Older

- T-scores are preferred.

  Grade: Fair-B-1

Rationale

The 2003 ISCD Official Positions (3) stated that for “Diagnosis in premenopausal women (age 20 to menopause) … Z-scores rather than T-scores should be used.” For “diagnosis in men … between age 50 and 65, T-scores may be used …” It is implied but not explicitly stated that Z-scores be used between the ages of 20 and 50 years. The ISCD recommendation to use Z-scores in young adults was, in part, intended to avoid misapplication of WHO criteria, which are based upon the T-score, to inappropriate populations (4). The WHO criteria were developed for postmenopausal white females, and extrapolation to other groups may not identify people at equivalent levels of fracture risk. In addition, it was felt that the Z-score might be more appropriate for non-white populations since the T-score is not adjusted for race on many densitometers. The issue of normative databases for non-white populations is dealt with elsewhere in this report. The use of Z-scores in children is an absolute necessity since children have not yet achieved peak bone mass and therefore T-scores are meaningless (4).

Discussion

Is There Much Difference Between T-scores and Z-scores in Younger Adults?

Assuming that bone density is relatively stable prior to age 50 (approximately the average age of menopause), there should be only minor differences between T-scores and Z-scores derived from ethnicity- and sex-matched reference population. There is no compelling scientific basis, therefore, for preferring one to the other in terms of bone density reporting. By extension, fracture outcomes cannot be used to adjudicate the choice and no other gold standard exists. The choice of one method of reporting over the other must, therefore, be based upon other considerations as discussed below.

An assessment of the difference between T-scores and Z-scores for major manufacturers (GE Healthcare, Hologic, and Norland) and measurement sites (lumbar spine, total hip, femoral neck, trochanter, 33% forearm) was undertaken for a 20-year old and 50-year old white man and woman (Table 2). As expected, in healthy young white adults (ages 20–50) there are relatively small differences between the respective T-score and Z-score for a given bone density measurement. At age 20, the difference between T-scores and Z-scores varies from +0.2 to −0.2. At age 50, the difference between T-scores and Z-scores varies from 0.0 to −1.4, with a mean of approximately −0.5. This means that at age 50, a Z-score of −2.0 is approximately equivalent to a T-score of −2.5. The same general findings were seen with men and women. Some differences were observed between equipment manufacturers. One contributing factor is the way of representing age-related change in BMD, typically either a polynomial model (quadratic or cubic) or linear model (bilinear or trilinear). Standardization among manufacturers in the mathematical approach would be beneficial. The use of different reference populations is another source of known inter-manufacturer variation (11). Standardization of hip measurements using the National Health and Nutrition Examination Survey (NHANES) III population (12) should reduce variation, but not all practitioners select the NHANES III reference data option. Manufacturers are encouraged to complete the conversion of NHANES III reference data for all hip sites in both genders.
Why Is BMD Testing Performed?

The initial measurement of BMD is usually performed for one of two very different reasons: to assess fracture risk and to assign a diagnostic classification. Older adults (postmenopausal women and men age 50 and older) may be at increased risk for fracture. T-scores more appropriately reflect short-term fracture risk than Z-scores, since Z-scores obscure the ‘normal’ age-related decline in bone mass which contributes to, but does not fully account for, the age-related increase in fractures. Conversely, determination of how an individual’s BMD has been affected by a metabolic risk factor is optimized by matching the reference population as closely as possible (at least for age, sex, and ethnicity), implying use of the Z-score.

Weight-adjustment of the Z-score is an option that is available on some instruments. The ISCD has previously recommended that weight-adjusted Z-scores be disabled on the software since their use will produce a more negative Z-score in overweight individuals despite the fact that they are not at greater fracture risk. Conversely, overweight individuals will have a better Z-score despite the fact that low body weight and body mass index are associated with greater risk for fracture (13,14). There are concerns regarding validation of the methods used for the Z-score weight-adjustment, uncertainty if the same adjustment applies to stable and changing weight, and lack of standardization among manufacturers. On balance, it is felt that the disadvantages of weight-adjusting Z-scores outweigh any theoretical advantages.

Table 2
Difference Between T-Score and Z-score (T Minus Z) According to Site, Gender, Age, and Equipment

<table>
<thead>
<tr>
<th>Software Version</th>
<th>Age 20</th>
<th>Age 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE Hologic Norland</td>
<td>v8.8 V 10+ Ver 2.9.0</td>
<td>v8.8 V 10+ Ver 2.9.0</td>
</tr>
<tr>
<td>White Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1–L4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>+0.1</td>
<td>0</td>
</tr>
<tr>
<td>Total hip</td>
<td>+0.1</td>
<td>0</td>
</tr>
<tr>
<td>Trochanter</td>
<td>+0.1</td>
<td>0</td>
</tr>
<tr>
<td>33% Radius</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1–L4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>+0.1</td>
<td>0</td>
</tr>
<tr>
<td>Total hip</td>
<td>+0.2</td>
<td>0</td>
</tr>
<tr>
<td>Trochanter</td>
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<td>0</td>
</tr>
<tr>
<td>33% Radius</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Values are ±0.1 due to rounding. Hip results based on NHANES III where available.

Age is a strong predictor of fracture risk that is independent of BMD. Since healthy young adults have low short-term fracture risk across a wide BMD spectrum (2,15,16), the use of a T-score (or Z-score) diagnostic cutoff of −2.5 does not have the same significance in a 30-year-old as in a 70-year-old. BMD measurement in healthy premenopausal women and men younger than age 50 cannot be used to assess short-term fracture risk and is only recommended to assess the skeletal impact of specific conditions. Conceptually, the Z-score is best suited to this purpose and avoids incorrectly labeling patients according to WHO criteria. The strongest argument in favor of reporting T-scores in young adults is to maintain a consistent approach across the age spectrum from young adulthood to mid-life and beyond, but this is not felt to outweigh the disadvantages.

For most biological variables that are normally distributed (as is BMD), a ‘normal range’ or reference range is defined as the normal mean plus or minus 2.0 standard deviations (SD). There is no compelling reason to define BMD differently than other variables. In other words, a 25-year-old who has a Z-score of −1.9 is below average but still within the expected range for age. Conversely, a Z-score that is 2.0 or more SD below the expected range for age should be considered abnormal.

III. Applicability of the WHO Densitometric Classification

ICSD Official Position

In Postmenopausal Women and in Men Age 50 and Older

- The WHO densitometric classification is applicable.

Grade: Fair-B-1

Rationale

The progressively increasing fracture burden experienced by women after menopause was the impetus for developing the WHO densitometric classification. Bone quality may deteriorate with age but this is not captured in bone densitometry measures. Younger adults with reduced bone mass do not have the same increased fracture risk as older adults with the same bone mass. Therefore, it is important to carefully consider the implications of applying the WHO classification to premenopausal women and men age 50 and older.

Discussion

Diagnostic Criteria and Clinical Recommendations

It is important not to confuse diagnostic thresholds with intervention thresholds. Although the WHO densitometric classification was explicitly designed for postmenopausal females, it was never intended to be a recommendation for the testing of all women at or after menopause, or that a T-score in the osteoporosis range should be used as the sole basis for initiating treatment. Rather, the WHO criteria provided a standardized basis for measuring and comparing the
frequencies of BMD in well-defined categories. The position of the ISCD is that BMD testing be considered for all women aged 65 and older and all men aged 70 and older, independent of other risk factors. Testing in younger individuals can be considered in the presence of other risk factors, though BMD measurement is usually not indicated in females prior to menopause or in men before age 50 years because of the low prevalence of significantly decreased BMD and low fracture risk (15). In women, common risk factors for a low BMD include premature menopause, chronic glucocorticoid therapy, family history of fragility fractures, and thin body habitus (17). In men, the three most common risk factors for low BMD include alcohol abuse, hypogonadism, and glucocorticoid therapy (18).

Is the WHO Densitometric Classification Broadly Applicable to Premenopausal Women and Younger Men?

Use of the WHO criteria in younger women and men is problematic since their actual fracture risk is much lower than at an equal level of BMD for an older individual. Whereas the 10-year fracture risk in a 70-year-old woman with a T-score of −1.0 is 11.5%, that of a 45-year-old woman with the same BMD would be three-fold lower, estimated at 4.3% (19). Similar conclusions are obtained by examining the corresponding data in men (9). The 10-year probability for sustaining an osteoporotic fracture (i.e., spine, hip, shoulder or vertebral) for a 45-year-old woman with a T-score of −2.5 at the hip is estimated at 8.1% (2). Such estimates increase to 16.2% in a 60-year-old woman, to 22.8% in a 70-year-old woman, and to 25.6% in an 80-year-old woman (15). The 10-year probability for sustaining any osteoporotic fracture for a 45-year-old man with a T-score of −2.5 at the hip is estimated at 6.3% (15). Estimates increase to 9.5% in a 60-year-old man, to 13.1% in a 70-year-old man, and to 18.7% in an 80-year-old man (15). Similarly, low bone mass has very different diagnostic and prognostic connotations, depending on a person’s age.

In view of the above, it is clear that the WHO diagnostic classification should not be applied broadly to premenopausal women or younger men. An additional problem in diagnosing osteoporosis in women prior to menopause is that reduced BMD frequently reflects low peak bone mass rather than high turnover bone loss. Therefore, the pathophysiology is quite different from that seen in postmenopausal osteoporosis. Pharmacologic therapy is rarely indicated in this group based upon BMD alone.

Can Specific Risk Factors Permit the Use of the WHO Densitometric Classification in Subgroups of Premenopausal Women and Younger Men?

In order to address this question, one needs to examine available information regarding fracture risk for a specified BMD in the presence of specific risk factors. The use of BMD or T-score as a single predictor of fractures has its limitations, because there are several powerful predictors of fractures that are independent of BMD. Other than age, the strongest risk factors are prevalent fractures and glucocorticoid therapy (20).

BMD testing may be requested because of the presence of fragility fracture(s). Premenopausal women and younger men are at such low risk for non-traumatic fractures, that in the absence of obvious clinical explanation (e.g., solid organ transplant on long-term glucocorticoids), this will normally merit a thorough evaluation for a diagnosis other than osteoporosis. Even the finding of unexplained reduced BMD (T-score below −2.5) is not sufficient for diagnosing osteoporosis since other conditions can also produce reduced BMD and fractures. In such cases, the diagnosis of osteoporosis is based mostly on the presence of a fragility fracture. The WHO classification is not helpful in quantifying fracture risk or making a specific diagnosis of osteoporosis in this population.

Long-term glucocorticoid therapy is another independent predictor of fractures (21). Randomized trials evaluating the efficacy of various bisphosphonates on preserving BMD have documented that patients on chronic glucocorticoid therapy tend to fracture at relatively higher BMD (T-score −0.7 to −1.7) (22). Some trials have included men and premenopausal women, although the majority of study participants were postmenopausal women. In a review by Roux et al (22), of four separate randomized glucocorticoid trials, the incidence of fracture in premenopausal women on glucocorticoid therapy was 0% (T-score between −0.3 and −0.7) whereas in men fracture incidence varied between 2–24% (T-scores between −0.5 and −1.7). Therefore, in these men on glucocorticoid therapy, but not premenopausal women, there was evidence of increased fracture risk. The published data, however, do not indicate which ages of men were at risk, and how this was modified by the duration and cumulative dose of glucocorticoids. It is not possible, therefore, to determine the general applicability of the WHO classification on densitometric diagnostic categories in adult men on glucocorticoids.

In theory, the presence of multiple independent risk factors for fracture could be used as the basis for applying the WHO classification. This might exploit flexible fracture risk assessment models, as opposed to rigid T-score thresholds. Such models could incorporate an individual’s risk profile, including BMD, to estimate individual risk for fracture over a finite time period (2); however, the influence of many of these risk factors on fracture risk has not been well characterized in younger adults (20).

In summary, current data do not support the use of the WHO diagnostic classification in selected premenopausal women or younger men, even when there are associated risk factors other than older age and postmenopausal status. No clinical risk factors, either singly or in combination, were identified that would alter this position.

At What Age can the WHO Densitometric Classification be Applied to Men?

Incident fracture rates in men demonstrate a bimodal distribution (23,24). An early peak in young men (age 20–30 years) that exceeds the fracture rate seen in young women
is felt to reflect the high rate of traumatic and sports-related injuries. Very few of these fractures affect the hip or spine, whereas there is a high rate of craniofacial fractures—a pattern inconsistent with osteoporosis. After approximately age 50–60 years, however, fracture rates in women exceed those in men, and both show a progressive increase at the fracture sites that are typical for osteoporotic women. Age-specific fracture rates in older men are consistently less than in women, however, with 10-year fracture rates lagging approximately 10–15 years behind those seen in postmenopausal women (15,24). This creates obvious challenges to diagnosing osteoporosis in young men. Even in middle-aged and older men, the benefits from targeted BMD testing or screening have not been well studied, therapeutic trials are still limited, and there is a need to better understand the effects and interactions of clinical risk factors on fracture risk in men.

Despite these differences between men and women, there are many more similarities. Older age, reduced BMD, low serum-free estradiol, alcohol excess, current smoking, low body weight, and frailty have each been associated with higher fracture risk in men and women (21,25–30). The BMD risk gradient (relative risk per SD) is similar in men and women, even if their absolute fracture risks differ (31–33); therefore, the differences between men and women are quantitative, not qualitative. There is value in having a diagnostic framework applicable to men and women of the same age so that prevalence of reduced BMD can be derived and compared. Given the broad acceptance of the WHO diagnostic classification for postmenopausal women, it is reasonable to apply the same framework to men starting at age 50, the approximate age of normal menopause. As noted above, this does not imply a need for testing simply because there is a diagnostic framework. The alternative position of delaying application of the WHO classification for men until age 60, 65, or 70 years was discussed but felt to complicate the approach unnecessarily, while restricting the epidemiologic objectives. It will be recalled from an earlier position in this document that T-scores (not Z-scores) be used in postmenopausal women and in men age 50 years or older. This creates a natural connection between the use of T-scores and application of the WHO densitometric classification while simultaneously avoiding the latter in premenopausal females and males under age 50, for whom Z-scores are preferred.

What Is the Clinical Approach to Osteoporosis by BMD Criteria in a Man Aged 50–69?

The management of this situation warrants discussion to ensure that the clinical approach considers some of the important differences between men and women. The clinical approach to a T-score of −2.5 or lower in a man aged 50–69 must be considered in the context of the clinical presentation. The usual reason for BMD testing in a man prior to age 70 years is a fracture. A fragility fracture is a risk factor for recurrent fractures, just as in women. There are at least three clinical syndromes associated with fractures in middle-aged men: low levels of IGF-I but normal growth hormone secretion (34), possibly related to specific alleles in the variable region of the IGF-I gene (35); low serum levels of free estradiol (36); and chronic hypercalciuria (37). For these men, fracture has clinical consequences and treatment is indicated.

What about those men with fracture who do not fit into the above syndromes? Men who are at risk are those with defined causes of secondary osteoporosis, most notably glucocorticoid-induced osteoporosis (GIOP). The extant guidelines for GIOP (38) would strongly recommend treatment for a man aged 50–69 on glucocorticoids, even if the man has a T-score greater than −2.5. For men with other treatable causes of osteoporosis, a case can be made to treat the underlying disorder and follow the bone density rather than treat the T-score. Other disorders that may warrant a bone density test in a man aged 50–69 would include hypogonadism, malabsorption, alcohol abuse, and hyperparathyroidism (39). In many cases, the underlying disorder can be treated. For those men without fracture, amelioration of risk factors (such as vitamin D deficiency, alcohol abuse, etc.) should be undertaken before starting other specific therapy for osteoporosis. For those men with fractures, unless there is a specific cause of osteoporosis amenable to treatment, medication for osteoporosis is indicated.

For men under age 70 without a specific indication, dual-energy X-ray absorptiometry (DXA) testing is not recommended. However, if the patient is tested and has a T score of −2.5 or less, evaluation for secondary causes of osteoporosis is recommended. For most patients, treatment of underlying disorders and risk factors plus a repeat DXA in two years will determine if bone loss is occurring. An unexplained T-score of −2.5 or less in a man age 50–69 or low trauma fractures usually warrants evaluation for secondary causes of osteoporosis.

IV. What Normative Database Should be Used for Non-White Individuals?

ICSD Official Position

- Z-scores should be population specific where adequate reference data exist. For the purpose of Z-score calculation, the patient’s self-reported ethnicity should be used.

Grade: Poor-C-1

Rationale

The previous ISCD position was to use a uniform white (non-race adjusted) female normative database for women of all ethnic groups, but this statement was limited to the USA population (5,40). No position was taken with respect to reference data or ethnicity-matching outside of the USA. The basis for these recommendations was, in part, based on the following: (a) defining ethnicity is often difficult, and (b) multi-ethnic fracture data indicated that the relative risk (RR) for fracture per SD reduction in peripheral BMD using a white, young-normal reference population database was
similar in five ethnic groups (white, African-Americans, Asians, Hispanics, and Native Americans) (41).

Discussion

The need for population-specific reference data in order to calculate T-scores is controversial. In part, this derives from differences in fracture rates and bone density that had been observed between countries and different ethnic groups, with a concern that T-scores derived from a single reference population may be inappropriate (12,42–45). Developing and updating young-adult and age-specific reference data for every combination of country, ethnicity, and gender on every bone density instrument is nearly impossible, and would challenge the economic resources of most countries while simultaneously creating a veritable Tower of Babel with enormous clinical confusion.

Technical Considerations

The use of population-specific reference data has unique problems. The major one is that only small differences in the SD of two different young-normal reference population databases creates large differences in the calculated T-score of patients or populations being measured, even when the same patients are measured on the same DXA manufacturer (46,47). Hence, the T-score may differ by more than 1.0 SD in the same patient measured at the same skeletal site on the same machine, when the T-score is calculated from two different healthy young-normal reference population databases. Much larger sample sizes are required to reliably estimate the population SD than the population mean peak BMD. The use of a standardized SD may reduce some of the expected variation that would arise through the use of different SD values, and is consistent with the principle of a similar gradient of risk (RR of fracture per SD) in different ethnic groups, even when absolute fracture rates differ (42).

There are many hurdles to be overcome in the establishment of ethnic-specific reference population databases. One of these hurdles relates to defining ethnicity. Ethnicity is far more than just skin color. Ethnicity is a complex interaction between gene-pool mixes, geography, and socio-cultural factors, and is difficult, if not impossible, to define clinically (48). Thus, a single racial group can show considerable ethnic diversity: just as calculating T-scores from two different white, young-normal reference population databases in the same postmenopausal white population will yield different T-scores, so will calculating the T-score from one ethnic, young-normal reference database and then re-calculating the T-score using a different ethnically-defined reference database. This can create clinical confusion, especially in nations where racial diversity is wide, where defining a specific ‘pure’ ethnicity is not easily accomplished, and where there is significant migration.

Clinical Considerations

An even larger hurdle to making specific reference database recommendations for non-white populations is the paucity of ethnic-specific fracture data, especially lifetime fracture risk. Hence, if the same principles whereby the WHO established their specific cut-points in the white, post-menopausal population (e.g., linking BMD prevalence to life-time fracture risk) were to be used in defining densitometric ‘osteoporosis’ in non-white populations, then the same methodology should be used. This is unlikely to be achieved in the near future.

Available data suggest that ethnicity-matched reference data may actually be misleading in terms of fracture risk assessment. Some populations (e.g., African Americans) have repeatedly been shown to have higher bone density and lower fracture rates (42,43). Differences in vertebral fracture rates in European countries are largely explained on the basis of differences in mean BMD and age (45). By contrast, hip fracture risk in Asians is lower than would be expected from considering BMD alone (42,49,50). Smaller skeletal size and/or differences in hip axis length appear to be a factor in the paradoxical relationship between BMD and fracture rates in Asians (51–55). There is evidence that racial size-disparity is actually diminishing due to secular changes in growth patterns (56,57). The use of a volume-adjusted BMD, such as bone mineral apparent density (BMAD), might be helpful in addressing issues related to size as they affect certain ethnic groups and patient populations (58–61). The technique for calculating BMAD would need to be standardized among manufacturers and integrated into software so that it could be easily applied in clinical practice; therefore, it is premature to develop a position related to BMAD.

Although it would be ideal to have a single reference database that could be applied globally, there are still some uncertainties over the global validity of this approach. It was felt to be premature to alter the existing ISCD position, which limits the recommendation to use a uniform white (non-race adjusted) normative database for deriving T-scores to the USA population. The situation with Z-scores is different since the objective is to compare a patient’s BMD with a closely matched normal population and not for fracture prediction (see earlier discussion); therefore, the use of population-specific (i.e., ethnicity-matched) reference data for deriving Z-scores is a global recommendation.

Where differences in the BMD-fracture relationship are identified, it cannot be assumed that population-specific reference data will reconcile the difference without direct proof. In fact, the enormous global variation in fracture risk (lifetime hip fracture risk for 50-year-old woman from 1% to 28.5% with 15-fold range in 10-year probability), greatly exceeds the variation in BMD; therefore, population-specific reference data will not reconcile all differences in the BMD-fracture relationship. Much more scientific study is needed to define where differences in fracture rates are (and are not) attributable to population-specific differences in BMD. It is likely that differences between human populations are smaller than differences within human populations. Therefore, a single reference database will probably suffice for most populations. As noted elsewhere in this issue, NHANES III is a reasonable standardized platform for hip BMD. Unfortunately, there is no equivalent for the lumbar spine or forearm. Since the
WHO absolute fracture risk project relies predominately on white population studies, it can be validly applied to white populations (2). Validation of the WHO absolute fracture risk method in non-white populations will be needed before this approach can be applied. Population-specific adjustments may be required where differences in fracture risk are not explained by the risk prediction model developed for white populations.

**In Summary**

The ISCD Official Positions stated in this paper attempt to resolve some of the limitations inherent in earlier ISCD Official Positions, as they relate to BMD reporting in groups other than white (Caucasian), postmenopausal females. While based on best available evidence, the data to substantiate the recommendation are incomplete. They will, however, evolve as the scientific evidence accumulates.

**References**