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Position Paper

An Update on the Diagnosis and Assessment of Osteoporosis with Densitometry

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Abstract. In 1994 the WHO proposed guidelines for the diagnosis of osteoporosis based on measurement of bone mineral density. They have been widely used for epidemiological studies, clinical research and for treatment strategies. Despite the widespread acceptance of the diagnostic criteria, several problems remain with their use. Uncertainties concern the optimal site for assessment, thresholds for men and diagnostic inaccuracies at different sites. In addition, the development of many new technologies to assess the amount or quality of bone poses problems in placing these new tools within a diagnostic and assessment setting. This review considers the recent literature that has highlighted the strengths and weaknesses of diagnostic thresholds and their use in the assessment of fracture risk, and makes recommendations for actions to resolve these difficulties.

Keywords: Definition of osteoporosis; Densitometry; Diagnosis; Risk assessment; Risk factors

Introduction

An increasing awareness of osteoporosis and the development of treatments with proven efficacy is likely to increase the demand for management of patients with osteoporosis. This in turn will require widespread facilities for its diagnosis and assessment. Measurements of bone mineral are a central component since this forms an integral component of the definition of osteoporosis.

The internationally agreed description of osteoporosis is 'a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures' [1]. The definition captures the notion that low bone mineral density is an important component of the risk of fracture, but recognizes that other abnormalities in the skeleton contribute to skeletal fragility. In addition, a variety of nonskeletal factors contribute to fracture risk [2–4]. Thus, the diagnosis of osteoporosis by the use of bone mineral density measurements is at the same time an assessment of a risk factor for the clinical outcome of fracture. There is a useful analogy with hypertension since blood pressure is used to diagnose hypertension which is in turn a major risk factor for stroke.

In 1994, an expert panel of the World Health Organization recommended thresholds of bone mineral density in women to define osteoporosis [4,5] that have been widely but not universally accepted by the international scientific community and by regulatory agencies [6–8]. Osteoporosis in postmenopausal Caucasian women is defined as a value for bone mineral density (BMD) or bone mineral content (BMC) more than 2.5 standard deviations below the young average value (Fig. 1). Severe osteoporosis (established osteoporosis) uses the same threshold, but in the presence of one or more fragility fractures.

The diagnostic threshold identifies approximately 15–20% of postmenopausal women as having osteoporosis

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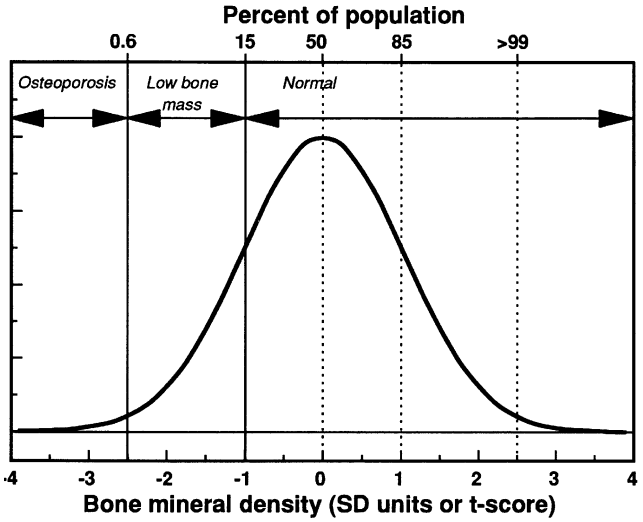

Fig. 1. Diagnostic thresholds for women based on the distribution of bone mineral density in the young healthy female population.

Table 1. Proportion (%) of white women with osteoporosis by age adjusted to 1990 US white women defined as a bone mass below 2.5 SD of the young adult reference range at the spine, hip or midradius.

Age range (years)	Any site	Hip alone
30–39	0	0
40–49	0	0
50–59	14.8	3.9
60–69	21.6	8.0
70–79	38.5	24.5
80+	70.0	47.5
$\geqslant 50$	30.3	16.2

when measurements using dual-energy X-ray absorptiometry (DXA) are made at the spine or the hip (Table 1) [5]. Given an approximately linear loss of BMD with age, and because of the Gaussian distribution of BMD values, the incidence of osteoporosis increases exponentially after the age of 50 years, as is also the case for many osteoporosis-related fractures. When measurements are made at the three sites most vulnerable to fracture (the hip, spine and wrist) approximately 30% of postmenopausal women would have osteoporosis (see Table 1). This approximates the average lifetime risk of these fractures.

Since the introduction of working definitions of osteoporosis, much attention has focused on their application to epidemiology, clinical trials and patient care. This paper reviews briefly the current strengths and in particular the limitations of diagnostic criteria. A major concern has been the poor concordance of measurements made at one site with measurements at another site, either with the same or different technologies. Many of these problems are due to errors of accuracy.

Errors of Accuracy

The objective of the diagnostic use of BMD is to measure as accurately as possible the true value which it was intended to measure. The 'true value in terms of the diagnosis of osteoporosis has been variously defined as the amount of skeletal calcium, bone density or BMD at the site measured or at another site. None of the absorptiometric techniques measure true bone density, but rather an areal bone density, in part due to the two-dimensional nature of the scan [9]. It is uncertain whether algorithms to adjust for this would improve the diagnostic or prognostic use of measurements [10,11]. Indeed, the two-dimensional nature of the scan captures an element of bone size that has an independent contribution to bone strength. A much greater limitation relates to other systematic errors.

Variable soft tissue densities are a particular problem with absorptiometric techniques applied to the spine and hip. The correction for fat makes a number of assumptions [12], particularly the assumption of homogenous disposition of fat in the body. Estimates of accuracy errors range from 2% for measurements at the forearm to 10% or more at other sites such as the spine measured laterally [13]. Absorptiometric techniques at the spine (anteroposterior) and hip which are most commonly used for diagnosis, incur accuracy errors of approximately 5%.

The accuracy of various techniques should be considered alongside the variance of measurements in the population to be examined, which ranges from 10% to 50% depending on the technique and site used for measurement and any normalization procedure applied. For absorptiometric techniques the variance (CV%) is no greater than 20%. It is evident, therefore, that techniques with high accuracy errors, say in the order of 5%, stratify individuals less certainly the smaller the population variance. For this reason it is expected that even if in reality there were perfect correlations between BMD at different sites, such errors of accuracy would result in large classification errors where thresholds of measured BMD are utilized to dichotomize the population.

Systematic inaccuracies also occur, particularly at the spine since the vertebrae are irregular in shape and apparent density and mineral content will depend in part upon the algorithm used for edge detection. Moreover, the underlying assumptions about the average fat to lean body mass ratio differ between manufacturers. Therefore different machines, even at the same site, give different results. For example, values for BMD at the lumbar spine using the Hologic device give values approximately 1 SD lower than values using the Lunar machine [14]. Notwithstanding, there are close correlations between the two methods at the spine [15]. A considerable advance has been the standardization of hip and spine measurements between different types of DXA equipment [15,16].

A further source of error relates to biologic variability. Bone is not a homogeneous structure and different sites have variable proportions of cancellous and cortical

bone. The problem is compounded by variable rates of bone loss at different sites with advancing age. This represents the 'biological' inaccuracy in predicting BMD at one site from measurements made at another site.

The size of the problem can be estimated knowing the accuracy errors and the correlation between sites. In the case of femoral neck and spine measurements, a typical correlation coefficient is about 0.6 with a standard error of estimate (SEE) of 0.14 g/cm^2 or 17%. Assuming that the accuracy error for the spine is 5.3% and for the neck is 6.5% [13] the expected SEE would be about 8.0% or a correlation coefficient 0.85. Such calculations suggest that about half the classification errors relate to technical errors of accuracy and the residual to biologic variability.

Irrespective of the source of errors, both these factors compound the problem that individuals deemed osteoporotic at one skeletal site may not be found to be osteoporotic at another [17–22]. Correlations between sites or between technologies at the same site are sufficiently poor (r^2 less than 80% in young health individuals and generally less than 50% in patients) to be of very low predictive value [18,23–25]. Even within the hip, correlation coefficients between regions are too low to be predictive. In one series, coefficients of determination (r^2) ranged from 29% to 94% [26]. In another study 10% of subjects categorized as having *osteoporosis* at one site were classified as *normal* at another [21], but the error rate in younger individuals is lower, in the order of 3% [27]. The same holds true in principle for hypertension, where measurements made at the leg may differ substantially from measurements made at the arm. One solution would be to designate individuals with osteoporosis at the spine but not at the hip as having osteoporosis of the spine, rather than using the term osteoporosis alone. This seems unsatisfactory for a systemic disease and confuses the field still further in much the same way as hypertension of the leg would do. It appears more appropriate, therefore, to select a standardized site for the purpose of diagnosis – not necessarily for risk assessment.

Different Methodologies of Assessment

The bone loss that occurs with age in women has been characterized in many population studies. The magnitude of premenopausal bone loss is controversial and may be site-dependent [28–30], but substantial bone loss occurs immediately after the menopause [31] and continues until old age [32]. However, the magnitude of the change with age in relation to the variance of the young adult population differs according to site and technique [20,33,34]. In terms of standard deviation units of change with age, highest rates of loss are seen with quantitative computed tomography (QCT), lateral DXA of the spine and phalangeal ultrasound velocity, and lower rates of change with some of the ultrasound attenuation methods at the heel. Intermediate rates of loss are seen with DXA of the forearm, anteroposterior spine and hip. For example, at the age of 80 years the average *T*-score by lateral DXA of the spine is –5, whereas for some heel ultrasound devices it may be as low as –2 standard deviation units [22]. In a large case–control study of individuals with and without fracture [35], the sensitivity of different techniques to 'detect' fracture cases varied more than 4-fold at a threshold of −2.5 SD (Table 2). It is thus clear that the *T*-score cannot be used interchangeably with different techniques and at different sites. Even within the hip, there is variation in the degree with which the *T*-score changes with age (Fig. 2). Indeed

Table 2. Proportion of women with spine fractures with a *T*-score of −2.5 SD or lower (sensitivity) according to the technique and site of measurement. Specificity denotes the proportion of women without fracture above the *T*-score threshold

Technique	Site	Sensitivity (%)	Specificity (%)
DXA	Spine	71.2	88.6
DXA	Femoral neck	33.8	97.2
DXA	Trochanter	24.9	98.2
QCT	Spine	94.2	58.6
QCT	Radius	17.7	98.3

From [35].

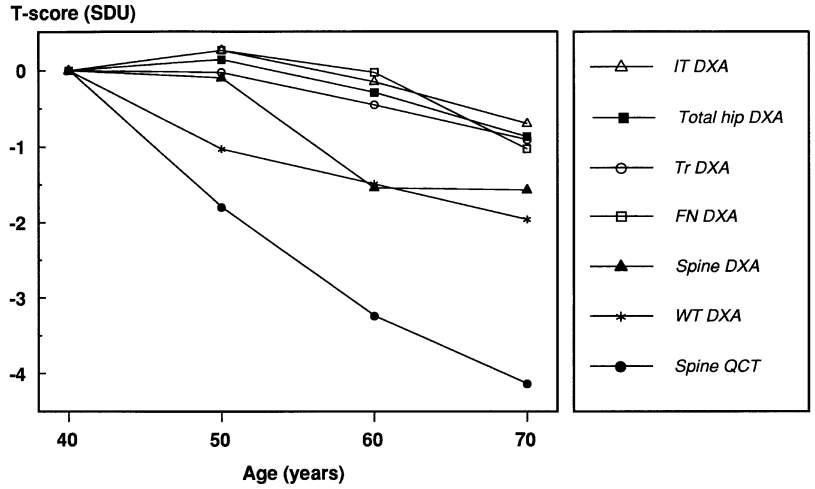

Fig. 2. T-score by age in healthy women according to site and technique. *IT*, intertrochanteric; *Tr*, trochanteric; *FN*, femoral neck; *WT*, Ward's triangle. After [26]

Table 3. Estimates of *T*-score and the prevalence of osteoporosis according to site and technique

Measurement site	Technique	*T*-score at 60 years	WHO classification	Prevalence of osteoporosis (%)
Spine	QCT	–2.5	OP	50
Spine	Lateral DXA	–2.2	LBM	38
Spine	DXA	–1.3	LBM	14
Fprear,	DXA	–1.4	LBM	12
Heel	Achilles	–1.5	LBM	11
Total hip	DXA	–0.9	N	6
Heel	Sahara	–0.7	N	3

From [22] and manufacturer's data
OP, osteoporosis; LBM, low bone mass; N, normal.

were the *T*-score to be used with different techniques, the prevalence of osteoporosis and proportion of individuals allocated to any diagnostic category would vary so much [22,36,37] as to devalue totally the credibility of the field of osteoporosis (Table 3.)

Diagnostic criteria have been published by the Japanese Society of Bone and Mineral Research [7]. Vertebral osteoporosis is defined on the basis of radiographic changes and a given decrement in BMD at a variety of skeletal sites and using different technologies. The approach used was to determine the measurement value that discriminated individuals with and without vertebral fracture with maximum sensitivity and specificity. A threshold value of 70% of the young adult mean value was chosen – a compromise value that accords best with data on lumbar BMD and least with measurements at the femoral neck. The approach does not resolve the underlying problems that relate to the bone biology and the natural history of osteoporosis. Moreover, the approach reduces the specificity of the test compared with the WHO cut-offs. In the case of hip fracture, for example, the WHO criteria for osteoporosis have high specificity for lifetime fracture risk (generally 80%) at the expense of low sensitivity (generally about 30%). Whereas this makes BMD assessments less suitable as a screening tool, it optimizes the identification of individuals truly at high risk. The Japanese approach may increase the sensitivity, but would expose individuals unnecessarily and erroneously to the consequences of a diagnostic label.

Other approaches to standardization are to equalize the apparent prevalence of osteoporosis with different techniques at the age of 65 years – midway through the age range where diagnostic assessments are commonly used in the clinic. Thus, all techniques would yield an identical estimate of the prevalence of osteoporosis at that age. However, techniques showing the less marked age-dependent changes in measurements would underestimate osteoporosis in the elderly and overestimate this at the time of the menopause. This would lead to overtreatment at the time of menopause when the risk is low and undertreatment in later life when the absolute risks are high. In addition, such standardization would not overcome the inherent misclassification errors intrinsic to the use of different sites and techniques.

The foregoing considerations suggest that 'gold standard' should be adopted in terms of site and technology for diagnostic purposes. No one technique or site subserves all the demands of densitometry, but if one technique is to be chosen for diagnosis and prognostic purposes the total hip or femoral neck are strong candidates. Measurements at the hip have the highest predictive value for hip fracture that has been well established in many prospective studies [38]. Moreover, it is the site of greatest biologic relevance, since hip fracture is the dominant complication of osteoporosis in terms of morbidity and cost. Several studies have shown that BMD of the femoral neck best predicts cervical fractures whereas the trochanteric site best predicts trochanteric fractures, but the total hip best reflects the risk of any hip fracture [39,40].

An argument can be made for using spinal BMD since this predicts the risk of any fracture as well or better than hip BMD in the perimenopausal population where hip fracture risk is low. In later life, however, spine measurements are confounded by osteoarthrosis whereas the hip is very much less affected [41,42]. At the end of the day, other techniques will continue to be used for diagnostic purposes. The individual with a fragility fracture and low BMD at the spine or other site is rightly characterized as osteoporotic irrespective of the value measured at the hip.

The WHO criteria were established largely with DXA in mind since this was the dominant technology at the time. The available evidence suggests that the diagnostic use of *T*-scores should be reserved for DXA at the hip. In the case of other sites and techniques, it may be preferable to express deviations of measurements from normal in units of measurement or units of risk. Examples of the latter include 5 or 10 year fracture risk (see later), or an age-standardized relative risk equivalent to a *T*-score, of say, –2.5 (e.g. RR = $2^{2.5}$ = 5.7 for hip fracture or $1.5^{2.5}$ = 2.8 for any fracture). This enfranchises the use of other techniques and sites for risk assessment. Indeed, where techniques give information on the likelihood of fracture, they can all be used in combination perhaps with other risk factors, to determine further investigation or treatment.

Choice of Reference Ranges

Reference ranges are commonly expressed in standard deviation units, in part because of the multiplicity of techniques and the systematic differences in BMD, even at the same site with different equipment. Recent attempts to standardize some sites, particularly the hip, may decrease the complexity of using criteria other than *T*-scores, but individuals will still be characterized differently according to the site measured and the technique used, the equipment and the reference population [43]. Population standard deviations of young healthy women vary from 10% to 20% depending on the technique used [22], so that an individual with a *T*-score of –2.5 can lie anywhere between 25% and 50% below the average young normal value. Discrepancies in the population standard deviation at different sites (and with different equipment) thus contribute to discrepancies in the *T*-score [23,34]. In one study where the same population base was used, the prevalence of osteoporosis in women aged 50 years or more ranged from 10.9% using DXA at the hip to 52.2% with DXA at the distal radius [7], largely due to differences in the population variance for these measurements. The apparent prevalence of osteoporosis also depends on the manner of expressing DXA results. The prevalence of osteoporosis at the lumbar spine is approximately 30% in women at the age of 70 years, but half that value when BMC rather than BMD is used [44].

The choice of a reference range is important for the accurate categorization of patients, as too is the estimate of the variance around the mean value. In choosing a cut-off value of –2.5 standard deviations, the intention of the WHO group was to make osteoporosis a rarity in healthy women before the menopause. Assuming a Gaussian distribution of BMD, 0.7% of the young adult population would be characterized as having osteoporosis.

In applying these concepts in practice a number of problems have arisen. Firstly, young adults used to calculate mean values and standard deviations may or may not include populations that are randomly selected, giving biased results. Also, reference data may exclude individuals with risk factors for bone disease. This will artifactually increase the mean value and reduce the standard deviation used to compute threshold values. In practice, reference ranges have been chosen variously from adults aged 20–29 years, 20–39 years, at the age of 50 years, etc., and these too have an impact on the apparent prevalence of osteoporosis [17,36,45]. Recently, US reference data for the hip have been generated from the NHANES III study and could serve as a standardization platform [46]. The use of NHANES III reference ranges derived from women aged 20 to 29 years and applied to the total hip decreases the apparent prevalence of osteoporosis in a reference population in the US from 49% using the femoral neck and laboratory reference ranges of Hologic to 28% [47], more in line with the thresholds envisaged by the WHO.

Should different countries or different races utilize their own reference ranges or would a common gold standard be sufficient? Normal ranges for DXA are available from many countries including Holland [48], UK [44,49], Germany [50], France [21] and USA [46] and several other European countries [51] where the difference in mean BMD and the standard deviations used are relatively small. The use of reference ranges in whites in the USA accommodates the higher bone mass and lower fracture risk in blacks [52].

Variations in BMD between populations appear to be substantially less than variations in fracture risk. Age- and sex-specific risk of hip fracture differs more than 10-fold, even in Europe [53–55]. These differences are very much larger than can be accounted for by any differences in BMD between these communities. Indeed, in Asia, hip fracture risk is lower than in Northern Europe or the USA but BMD is lower [45,56]. In view of the disparity between population fracture risks and BMD, it is uncertain whether reference ranges should be drawn from local populations. There is a case, therefore, particularly for simplicity, for adopting an international reference range and standard deviations, such as the NHANES material, until further work tempers this view. The same holds true for other diagnostic methods, in that reference ranges should be derived from large population bases appropriate for international use.

The reference ranges utilized for the diagnosis of osteoporosis are suggested for women. Cut-off values for men have variously used values derived from the female or from male populations. Not surprisingly the prevalence of osteoporosis is greater using male-specific ranges at the hip [52]. In men, the risk of fracture is substantially lower for a bone mineral measurement within their own reference range, so that a more stringent criterion is appropriate to yield the same risk as in women [3,52]. The use of the same absolute value of BMD as a cut-off men as that used in women gives approximately the same absolute risk of vertebral and of hip fracture [57–59]. For this reason it may be appropriate from both a scientific and pragmatic view to utilize the same absolute threshold in both men and women, but it is important to recognize that the data on men are scanty and not all studies show comparable gradients of fracture risk with BMD in men [60].

Risk Assessment

If diagnostic criteria for osteoporosis are confined to DXA at the hip, then how should we utilize measurements made at other sites or measurements made with other techniques? Several considerations indicate that these alternative methods of assessment have an important role in risk assessment, if not for diagnosis.

The performance characteristics of many measurement techniques have been well characterized [3,38,61]. For the purposes of risk assessment the characteristic of central importance is the ability of a technique to predict

fractures. This is traditionally expressed as the increase in relative risk per standard deviation unit decrease in bone mineral measurement.

There are significant differences in the performance of different techniques at different sites. In addition, the performance depends on the type of fracture [38]. For example, BMD assessments by DXA to predict hip fracture are better where measurements are made at the hip rather than at the spine or forearm (Table 4). An individual with a *T*-score of –3 SD at the hip would have a 2.6^3 or greater than 15-fold higher risk than an individual with a T-score of 0 SD. Where the intention is to predict any osteoporotic fracture, the commonly used techniques are comparable. The risk of fracture increases approximately 1.5-fold for each 1 SD decrement in measurement. Thus, an individual with a measurement 3 SD below the average value for age would have a 1.5^3 or greater than 3-fold higher risk than an individual with an average BMD. Although the total risk is less than for hip fracture, it would exceed treatment thresholds envisaged by most [62–64]. Thus, these techniques have a utility independent of any diagnostic test but they also have the potential to be used diagnostically, since they measure an aspect of bone captured by the definition of osteoporosis. The challenge is how to express the clinical information they derive in a manner useful to the clinician.

The consideration of other risk factors in conjunction with BMD assessments also improves the predictive value of the test [2,65]. Examples are given in Table 5 of factors that contribute significantly to fracture risk over and above that provided by bone density measurements or age. Thus, the presence of multiple risk factors can be used to enhance a case-finding strategy in osteoporosis [66]. Indeed, this general strategy has been incorporated into practice guidelines around the world [62–64]. Thus, the presence say of low ultrasound attenuation or velocity, together with independent risk factors, might qualify individuals for treatment, without the need for BMD assessment at the hip. In other words, it is the risk of fracture that is important rather than the fulfilment of a diagnostic criterion. A caveat is that some risk factors are not amenable to particular treatments so that the relationship between total risk and reversible risk is important. Liability to falls is an appropriate example where the risk of fracture is high but treatment with agents affecting bone metabolism may have little effect on risk [67]. Other risk factors such as prior fragility fractures contribute to a risk that is responsive to interventions. The principle of assessing risk is well demonstrated in the case-finding strategy of the National Osteoporosis Foundation [63], where intervention thresholds based on BMD assessment with DXA at the hip are modified according to the presence of risk factors.

In other countries a more conservative view is taken in that patients with osteoporosis are offered treatment [62]. The presence of risk factors provides the opportunity to direct individuals for assessment by DXA. Whereas clinical risk factors are traditionally used (e.g., low body mass index, premature menopause, corticosteroid use), the wide availability and proliferation of peripheral densitometry and quantitative ultrasound (QUS) devices suggest that, where low values are found, these might be used to trigger the more formal assessment with DXA at the hip. A middle road between these approaches is a strategy of triage in which individuals at very high risk would qualify for treatment, those at very low risk would not be further evaluated, and only those at intermediate risk would have further assessment by DXA at the hip [68].

Table 4. Relative risk (with 95% confidence interval) of fracture in women for a 1 SD decrease in bone mineral density (absorptiometry) below the age-adjusted mean

Site of measurement	Forearm fracture	Hip fracture	Vertebral fracture	All fractures
Distal radius	1.7 (1.4–2.0)	1.8 (1.4–2.2)	1.7 (1.4–2.1)	1.4 (1.3–1.6)
Femoral neck	1.4 (1.4–1.6)	2.6 (2.0–3.5)	1.8 (1.1–2.7)	1.6 (1.4–1.8)
Lumbar spine	1.5 (1.3–1.8)	1.6 (1.2–2.2)	2.3 (1.9–2.8)	1.5 (1.4–1.7)

From [38].

Table 5. Examples of relative risks of hip fracture in women with and without adjustment for BMD

Risk assessment	Relative risk	
	Crude	Adjusted[a]
Hip BMD 1 SD below mean population value	2.6	
Non-carboxylated osteocalcin above normal	2.0	1.8
Biochemical index of bone resorption (CTX) above premenopausal range	2.2	2.0
Prior fragility fracture after the age of 50 years	1.4	1.3
Body weight below 57.8 kg	1.8	1.4
First-degree relative with a history of fracility fractures aged 50 years or more	1.7	1.5
Maternal family history of hip fracture	2.0	1.9
Current cigarette smoking	1.9	1.2
Poor visual capacity ($<2/10$)	2.0	2.0
Low gait speed (per 1 SD decrease)	1.4	1.3
Increase in body sway (per 1 SD)	1.9	1.7

From [65].
[a]Adjusted for BMD.

Assessment and Treatment Thresholds

Thresholds used to characterize multifactorial diseases are often arbitrarily defined. In the case of osteoporosis, fracture risk increases continuously with decreasing BMD (Fig. 3) [69] so that there is no biologic breakpoint to characterize absolutely an individual who will fracture from one who will not. Nevertheless thresholds are useful in a clinical perspective, where they give

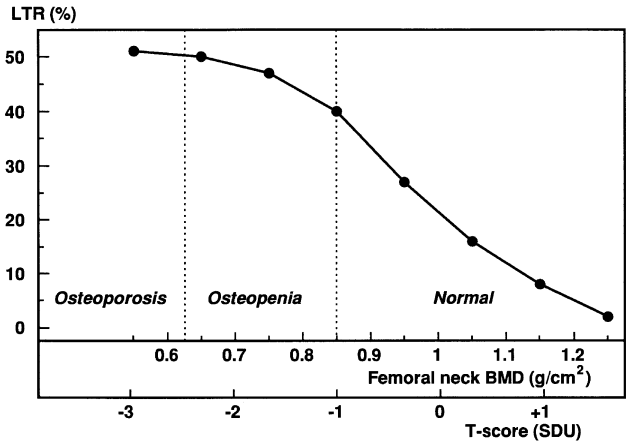

Fig. 3. Remaining life-time risk (LTR) of hip fracture in Swedish women aged 50 years according to BMD at the femoral neck.

information on prognosis or treatment. In the case of BMD assessment both types of information are given, but need to be interpreted cautiously [70,71].

In the case of diagnostic thresholds, it is relevant to recall that a positive (or negative) test may be spurious. The finding of a low BMD should raise the question of why this is so, and other causes of low BMD (technical, confounding and clinical) should be excluded to fulfill a diagnostic criterion. Also, because the same diagnostic threshold in one country will not identify individuals with the same fracture risk in another country with an identical *T*-score, it is important not to confuse diagnostic thresholds with treatment thresholds. This was not the intention of the WHO, but the diagnostic criterion is interpreted by many practitioners and healthcare agencies as an intervention threshold. But intervention thresholds depend not only on risk which varies with age, but also on the benefits and costs of interventions.

The notion that intervention thresholds may differ from diagnostic thresholds requires the elucidation of intervention thresholds for osteoporosis in much the same way as cardiovascular disease [72]. This will demand the conversion of relative risks into absolute risks. An example of absolute risks is given in Table 6. If an intervention threshold were set (for example) as a 10-year risk of hip fracture that exceeded 10%, this threshold would be attained in women with osteoporosis at the age of 65 years or more. The same threshold of risk is attained in an average population of women aged 75 years or more. If multiple risk factors are to be used to maximum advantage the interdependence of all risk assessments will require elucidation. Such approaches will preserve the utility of the *T*-score for diagnosis with DXA at the hip and enhance the value of all technologies in enfranchising the populations most at risk from fractures.

Evolution of Diagnostic Guidelines

The field of osteoporosis is enriched with respect to technologies and potential sites for diagnosis and assessment. The price to be paid is the knowledge that one test at one site can never be exactly predictive of the other. Two approaches are worthy of consideration. The first is to acknowledge DXA at the hip as the 'gold-standard' of today for providing a diagnostic test and to maintain the WHO classification for this use alone. In this context the performance characteristics of other techniques or sites (sensitivity, specificity, positive predictive value) to identify individuals with osteoporosis or low bone mass at the hip should be determined. This would provide a basis for assessing clinical utility. For example, most clinicians would accept a result for clinical decision-making that showed an 80% probability that an individual had osteoporosis.

Ultimately it is desirable to have measurements of all techniques expressed in units of risk. Absolute risks are appropriate and preferable to relative risks. For example, a relative risk of hip fracture of 1.0 (i.e., average risk) equates with a 10-year probability of 0.4% in women aged 45 years but to 16% at the age of 85 years. Such approaches will ultimately enfranchise all technologies

Table 6. Ten-year probability of hip fracture in Swedish men and women according to age and BMD at the femoral neck

	Men				Women			
Age (years)	Population	*T*-score –1	*T*-score –2.5	*T*-score ⩽–2.5	Population	*T*-score –1	*T*-score –2.5	*T*-score ⩽–2.5
45	0.5	0.7	2.2	3.4	0.4	0.4	1.4	2.2
50	0.8	1.1	3.4	5.1	0.6	0.5	1.7	2.9
55	0.8	0.9	3.1	4.9	1.2	0.7	2.9	4.9
60	1.2	1.2	3.7	6.0	2.3	1.1	4.4	7.8
65	2.1	1.9	5.3	8.8	3.9	1.5	5.9	11.3
70	3.4	2.7	8.5	14.3	7.3	2.0	8.8	18.3
75	5.9	4.1	14.2	24.2	11.7	2.3	11.1	24.6
80	7.6	4.6	13.7	24.3	15.5	2.5	11.5	27.9
85	7.1	7.6	10.5	19.9	16.1	2.1	10.0	25.8

J. A. Kanis, O. Johnell and A. Oden, unpublished data.

of predictive value including clinical risk factors. This will demand an examination of the independence of all these factors into suitable models. It will also demand that clinicians and regulatory agencies accept the notion that a given risk of osteoporotic fracture provides a diagnostic or intervention threshold. Since these developments will take time, manufacturers should consider the necessity in the interim to express measurements as probabilities of disease category and where possible risk of fracture compared to average risk with or without recourse to the *T*-score.

Conclusions

The strength of the WHO criteria lies in the uniformity of approach. It is important that different segments of the community are given the same message concerning the prevalence, incidence and epidemiology of osteoporosis.

Variations in skeletal composition and limitations in the diagnostic accuracy of techniques indicate that measurements made at one site have only limited predictive value for measurements at another. The same holds true for different techniques, even when taken at the same site. There is, thus, a strong case for standardization. The site that appears optimal in this regard is the total hip since it has the highest predictive value of all current techniques assessed prospectively. Moreover, the hip is less adversely affected than the spine by osteoarthrosis and osteoarthritis with age [38] and, despite the disparity between DXA techniques, absolute values have been standardized for the hip. If the hip is to be used as a reference site, the same absolute value for BMD can be applied to men as is the case for women for diagnostic criteria. The development of new techniques with higher predictive value than DXA at the hip would clearly temper this view.

It is important to re-emphasize that diagnostic thresholds are not necessarily intervention thresholds. Clinical medicine is perfectly used to having different intervention thresholds depending on other risk factors. A good example is the management of hyperlipidemia, where intervention thresholds depend on other risk factors such as blood pressure and age [72].

The foregoing considerations do not preclude the use of other technologies in risk assessment. Intervention thresholds will depend upon risk, life expectancy, and the benefits and side effects of interventions. Within this framework all risk assessments have their use. DXA at the forearm, spine and hip have the same predictive value for any fracture (see Table 3) and in this context have equal validity. Also, there is intuitively no specific reason why diagnosis (using DXA at the hip) must be made in order to direct interventions. Good examples would be the presence of fragility fractures, or the combination of low ultrasound values with clinical risk factors.

Summary and Recommendations

1. The WHO has provided diagnostic criteria for osteoporosis and low bone mass (osteopenia) based on bone mineral density (BMD) measurements.
2. Osteoporosis is defined as a BMD 2.5 SD or more below the young average value in women. Severe osteoporosis (established osteoporosis) uses the same threshold, but in the presence of fragility fractures. We recommend that these diagnostic criteria are maintained.
3. Diagnostic thresholds have been best validated at the hip with dual-energy X-ray absorptiometry (DXA). BMD measurements at this site predict hip fractures as well as blood pressure predicts stroke and significantly better than serum cholesterol predicts myocardial infarction. Hip BMD predicts other osteoporotic fractures as well or better than measurements at other sites with DXA or the use of other densitometric techniques.
4. The use of the *T*-score requires a comparison of the measurement with measurements in a young reference population. Although fracture risk varies between populations there is insufficient knowledge at present to recommend that local reference ranges be used. It is recommended that the NHANES III data base be used as an international reference until further research changes this view.
5. Using the age 20–29 years as the age of the young healthy population yields prevalences of osteoporosis similar to those published by the WHO and is in keeping with the recommendations of the International Committee for Standards in Bone Measurement. We recommend that these thresholds be used.
6. The relationship between BMD and hip fracture risk is similar in men and women though the data are scanty. We recommend that the same diagnostic thresholds be used in men – namely a BMD at the hip that lies 2.5 SD or more below the reference range for young women – until further research changes this view.
7. Measurements at other sites correlate with hip BMD but not sufficiently closely that they can be used for predictive purposes. This is due to biological variability between sites and errors of accuracy.
8. Compared with DXA at the hip, measurements at other sites and particularly with other techniques gives differences in the variance around population means and in apparent rates of bone loss. These differences mean that the use of the *T*-score yields different information on risk and populations at risk compared with DXA at the hip. *T*-scores cannot be used interchangeably, therefore, between sites and techniques.
9. We recommend that the diagnostic use of *T*-scores be reserved for DXA at the hip.
10. Many validated techniques in addition to DXA have given information on fracture prediction from cross-sectional or prospective studies. They also provide

relevant information on bone density status at the measurement site. Due to the lack of established diagnostic criteria they should be used for risk assessment or in combination with other risk factors to direct interventions to those at high risk. Indeed, decisions to treat should be based on a comprehensive assessment of the risk of fracture rather than the fulfilment of a single diagnostic criterion – an approach acknowledged in current practice guidelines.

11. Thus, all validated densitometric (and ultrasonic) techniques can be used as tools for assessment and to aid treatment decisions. To this end their utility lies in providing information on risk. We recommend that numerical output of densitometric devices is expressed as fracture risk irrespective of whether this is alongside densitometric values (e.g. g/cm^2, *T*-scores or *Z*-scores.
12. The risk of fracture at different sites can be computed from the gradient of risk for fracture for each 1 SD decrement in measurement. Risk estimates from well-designed cross-sectional studies might produce comparable results for short-term prediction for some types of fractures and may be adequate, therefore, for this purpose.
13. Absolute risk is preferable to relative risks but if relative risks are to be used they should be adjusted to population risks. Lifetime risks are inappropriate for decisions on treatment, since lifetime treatments are not envisaged or practicable. Ten-year risk accommodates the anticipated duration of treatment (3–5 years) and the slow offset time documented for several interventions when treatment is stopped (e.g., gonadal steroids and bisphosphonates). Lifetime risks may be suitable for counselling patients.
14. Ideally, the risk of all osteoporotic fractures should be evaluated, but there are large gaps in our knowledge of these risks worldwide. Hip fracture probabilities are well documented in many regions of the world and 10-year risks for hip fracture are an appropriate interim measure.
15. Improvements in risk assessment can be achieved by the use of multiple risk factors. There is, however, a need to examine the interrelationship of all risk factors and their applicability on an international basis.

Appendix. Members of the Committee of Scientific Advisory Board

Jonathan D. Adachi (Canada), Silvano Adami (Italy), Roberto Arinoviche (Chile), John Bilezikian (USA), Jean-Philippe Bonjour (Switzerland), Aurelio Borelli (Brazil), Maria Luisa Brandi (Italy), Narong Bunyaratavej (Thailand), Daniel Chappard (France), Claus Christiansen (Denmark), Juliet Compston (UK), Cyrus Cooper (UK), Pierre Delmas (France), Martina Doren (UK), Marie Christine deVermejoul (France), Jean Pierre Devogelaer (Belgium), John Eisman (Australia), Erik Fink Eriksen (Denmark), Dieter Felsenberg (Germany), Jose Luis Ferretti (Argentina), Herbert Fleisch (Switzerland), Carlo Gennari (Italy), Piet Geusens (Belgium), Claus C. Glüer (Germany), Shi-fu Guo (China), Stephen Hough (South Africa), Olof Johnell [Vice-Chairman] (Sweden), John Kanis (UK), Jean Marc Kaufman (Belgium), Sundeep Khosla (USA), Edith Lau (China), Uri Liberman (Israel), Paul Lips (The Netherlands), Sverker Ljunghall (Sweden), Roman Lorenc (Poland), Frank Luyten (Belgium), George Lyritis (Greece), Michael McClung (USA), Daniel Messina (Argentina), Pierre Meunier (France), Paul Miller (USA), Hajime Orimo (Japan), Sergio Ortolani (Italy), Socrates Papapoulos (The Netherlands), Mario Passeri (Italy), Gyula Poor (Hungary), Christine Poullart (Belgium), Jonathan Reeve (UK), Jean Yves Reginster (Belgium), lain Reid (New Zealand), Johann Ringe (Germany), Rene Rizzoli [Chairman] (Switzerland), Christian Roux (France), Graham Russell (UK), Ego Seeman (Australia), Markus Seibel (Germany), Alan Silman (UK), Jan Stepan (Czech Republic), Jorge Morales Torres (Mexico), Nelson Watts (USA), Christian Wüster (Germany).

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