Rev Endocr Metab Disord (2006) 7:75–89
DOI 10.1007/s11154-006-9006-0

Guidelines for the diagnosis of osteoporosis: T-scores vs fractures

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Published online: 22 December 2006

Abstract The development of bone mineral densitimometry methodologies, especially central dual energy X-ray absorptiometry (DXA) methods have allowed this quantitative tool to be used to diagnose osteoporosis before the first fragility fracture has occurred. The World Health Organization osteoporosis working group set the stage for the BMD cut-off criteria development. The wide application of DXA has brought the treatment of osteoporosis to the primary care level, a very necessary step if this increasingly prevalent disease is to have a decline in its incidence. The most difficult osteoporosis cases, for which there are many and their associated difficult DXA results and interpretation will always require specialists' involvement. In particular, the embracement of the WHO absolute fracture risk validated project will take DXA to a much greater level of value in making management decisions. In particular, the WHO absolute risk data will allow physicians, health–economic policy makers, and payors of medical services to come closer together to decide which patients are at a level of unacceptable fracture risk that justifies treatment intervention. The implementation of this validated project will also remove the unacceptable subjective computer printouts on DXA reports that often lead to the over-treatment of low risk patients and at times the under-treatment of high risk patients. The evolution of the clinical interpretation of bone densitometry has been a work in progress. Challenges in the clinical measurement of bone strength remain and will also evolve. The field of osteoporosis has grown with the use of DXA and will continue to embrace this technology as other technologies to measure fracture risk become applied in clinical practice.

Keywords Bone densitometry · DXA · T-scores · World Health Organization · WHO · Reference population databases · Postmenopausal osteoporosis · Osteoporosis risk assessment · WHO absolute risk · Absolute fracture risk · Osteoporotic risk factors

Bone mineral density (BMD) measurements have provided the basis for making the diagnosis of postmenopausal osteoporosis (PMO) by BMD criteria. BMD measurements have also been the anchor for the prediction of fracture risk in the postmenopausal female and elderly male populations.

Intervention decisions (e.g., treatment of PMO) are intimately linked to bone mineral density measurements, especially at the central sites (spine and hip) by dual energy X-ray absorptiometry (DXA). BMD measurements, along with increased age, form the foundation for the basis of the 10-year absolute global (all) fracture risk model being developed by the World Health Organization (WHO), into which other validated risk factors are incorporated into the equation to increase risk prediction

Nevertheless, ever since the creation of the BMD (T-score) criteria for providing a diagnosis of postmenopausal osteoporosis, there have been many misunderstandings and misuses of the WHO criteria—especially the misconception that if the "T-score" is not below −2.5 SD a patient may not have osteoporosis even in the face of a prevalent fragility fracture. In addition, many payors for health care services as well as health care providers mistakenly assume the T-score is the intervention (treatment) threshold. At best, the WHO criteria were intended to be a diagnostic, not intervention threshold. In this regard, since the majority of postmenopausal women and elderly men develop fragility

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fractures who do not have osteoporosis by WHO criteria, many at-risk patients may not receive treatment for skeletal fragility because their T-score is not −2.5 or lower. The following discussion will hopefully put these important issues into proper context.

1 Using DXA for the diagnosis of osteoporosis

In 1992 a working group of the WHO met to attempt to utilize BMD measurements of the spine, hip and forearm to define the prevalence of osteoporosis in the postmenopausal population. Justification for the utilization of a BMD measurement to make a diagnosis of osteoporosis was the recognition that the lower the BMD level, the higher the risk for fragility fracture; and, that once the first fracture has occurred, the risk for the subsequent fracture is extremely high [1, 2] (Fig. 1). Hence, one of the goals of the WHO working group was to provide a BMD level where the "diagnosis" of osteoporosis could be made before the first fragility fracture has occurred, not to provide a number that would be associated with a fracture risk great enough to consider intervention to prevent the first fracture. The major global perspective of the WHO working group was that of deciding a BMD level to diagnose postmenopausal osteoporosis in order to advise nations as to the potential economic burden that PMO-fractures could be anticipated to consume of their gross domestic product (GDP). In order to provide a BMD threshold for the diagnosis of PMO, the WHO working group had to decide upon a BMD value that was appropriate for the diagnosis of osteoporosis in the postmenopausal population. Data from the United Kingdom and the United States comparing population-based BMD to life-time fracture risk in Caucasian postmenopausal women age 50 and older was used. The WHO working group agreed upon a BMD threshold which utilized the number of standard deviations below the young–adult mean value (ultimately called a "T-score") of −2.5 for the diagnosis of PMO at the population level [3]. This value captured 30% of the postmenopausal population with a T-score of −2.5 or below at the hip (femoral neck), anterior–posterior lumbar spine, or forearm which matched the life-time risk for fracture at any of these three skeletal sites in these populations. In addition, examining the femoral neck alone, 16% of these populations were at or below −2.5 which also corresponded to the life-time risk of hip fracture (16%). Hence, the prevalence of PMO created by the chosen threshold matched the observed lifetime fracture risk and, thus, the −2.5 threshold was chosen.

Obviously, the prevalence of osteoporosis can be influenced by the T-score (SD) cut-point chosen, since the T-score is calculated from the young-normal reference population database and small differences in the SD of the *young-normal reference population database substantially* impact the calculation [4] (*Table 1, Faulkner et al. JCD*). In 1992 the preliminary cut-point suggested was a T-score of −2.0 for the diagnosis of PMO and preliminary calculations of the prevalence of PMO were made [5]. In 1994 when the final cut-point of a T-score of −2.5 was agreed upon the prevalence of PMO worldwide was re-calculated [6].

The T-score, based on an SD value, was used rather than absolute BMD (g/cm^2) because the different calibrations of devices from the three major manufacturers of central DXA machines would have required device-specific BMD values.

The substitution of the T-score mitigated some, but not all, of the differences among DXA devices. Differences in T-scores may also exist in the same patient when calculated from different DXA machines even at the same skeletal site (e.g., spine or forearm) since the spine and forearm reference population databases are manufacturer-specific [7–9]. The T-score discrepancy among DXA manufacturers at the hip was removed when all manufacturers incorporated the only non-proprietary consistent young-normal reference population database, the NHANES III (National Health and Nutrition Education Survey III) [10–12]. There remains an approximate 0.3 SD difference among manufacturer T-score calculations at the spine or by central DXA and even larger differences at the forearm by central DXA or any peripheral BMD device or central quantitative computerized tomography (QCT). The peripheral devices and central (spine) QcT are very accurate measurements and do predict fracture risk but the T-score discrepancies is in large part a database issue [4, 13, 14] (Fig. 2, Faulkner et al. [8]).

Despite these limitations, the T-score rapidly became the basis for the clinical application of DXA for the diagnosis of PMO. [15, 16]. The T-score provided the clinician with the ability and opportunity to diagnose osteoporosis before a fracture occurred, an important advance because of the large increase in subsequent fracture risk conferred by the first fracture, independent of the BMD. In this manner, the T-score came to be used in patient management much as other surrogate markers for disease outcomes had been previously used in the management of otherwise asymptomatic patients such as the surrogate markers of blood pressure and cholesterol for the outcomes of stroke and myocardial infarction, respectively. If a postmenopausal woman was found to have a T-score of −2.5 or poorer at the hip, spine or forearm and the WHO criteria applied, a diagnosis of osteoporosis and subsequent management decisions could be made with the intention of preventing the first fracture. There has been a cascade of positive impacts on osteoporosis awareness and legislation as a result of the WHO osteoporosis working group publications. In 1997 in the United States, the Bone Mass Measurement Act formed the basis for wider Medicare reimbursement of bone mass measurements [17]. In 2002 The United States Prevention

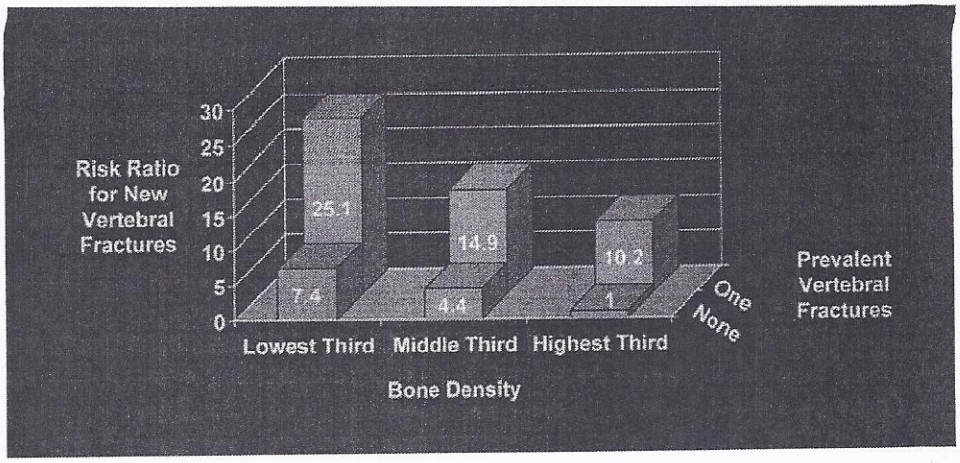

Fig. 1 The combined effect of bone density and prevalent fractures on the risk ratio for new vertebral fractures (Adapted from data reported in Ross et al. [2])

Services Task Force (USPSTF) endorsed population screening for PMO, the second disease state (the first: breast cancer screening) where population screening (as opposed to case finding strategies) was embraced [18]. Then, in 2004, the first US Surgeon General's report on the status of America's skeletal health reinforced the USPSTF recommendation-BMD testing as a pivotal component for the assessment of the at-risk postmenopausal population (60 years and older) [19]. There are other guidelines for the use of bone density in case finding strategies in the United States from different organizations for the entire postmenopausal population, even under the age of 60 years. The National Osteoporosis Foundation (NOF) guidelines for the postmenopausal population have been widely embraced: test all postmenopausal women aged 65 and older regardless of risk factors and under age 65 years with additional risk factors [20]. The guidelines for BMD measurements in a variety of clinical circumstances have been provided by the American Association of Endocrinologists, The North American Menopausal Society, The American Colleges of Rheumatology and Obstetrics/Gynecology, and, The International Society for Clinical Densitometry (ISCD). The ISCD recommendations are outlined in Table 2 [21, 22].

The WHO working group on PMO also described a second diagnostic category, osteopenia. This category was defined as a T-score of −1.0 to −2.5 measured at the spine, hip or forearm. Justification for the creation of this category between normal and osteoporosis is to provide a clinical explanation of the fracture risk gradient—as BMD declines, risk for fracture increases and the curve addressing this relationship is an exponential one [23] (Fig. 3). Despite the fact that the lower the BMD the greater the risk; and, that the relative risk for fracture approximately doubles for each SD that the BMD is below the young-normal mean or population mean BMD levels, data from population studies have consistently shown that more postmenopausal women and elderly men whose BMD levels are in the osteopenic range as opposed to the osteoporotic range have fragility fractures regardless of whether the measurement is made by a peripheral or central BMD measuring device [24–28] (Fig. 4) [24] and (Fig. 5) [28]. The results are probably due to the fact that many more people are osteopenic than are osteoporotic and there are simply more fractures in this larger population. In addition risk factors for fracture independent of low BMD also contribute to fracture risk; and, if present along with a low BMD may lead to a high fracture risk even with "T-scores" that are not in the WHO osteoporotic range.

The introduction of the label "osteopenia" has been criticized. The criticism is justified when the label of osteopenia is applied to low risk postmenopausal women, who may consequently be overtreated with pharmacological interventions, when evidence of a benefit/risk reduction is

Table 1 Influence of variable population standard deviation (SD) on T-score at constant BMD

SD=10%	SD=15%	SD=20%	T-score difference (SD)
(0.90–1.0)/0.10=T: −1.0	(0.90–1.0)/0.15=T: −0.7	(0.90–1.0)/0.20=T: −0.5	0.5
(0.80–1.0)/0.10=T: −2.0	(0.80–1.0)/0.15=T: −1.3	(0.80–1.0)/0.20=T: −1.0	1.0
(0.70–1.0)/0.10=T: −3.0	(0.70–1.0)/0.15=T: −2.0	(0.70–1.0)/0.20=T: −1.5	1.5

Originally published in Melton et al. [4].

weaker than in postmenopausal women with osteoporosis. In addition, younger, low-risk "osteopenic" women are given a diagnostic label that may be detrimental to their quality of life and inhibit their ability to obtain health-care coverage.

Despite the value of the WHO classifications to increase international awareness of PMO, there are acknowledged limitations:

1. The application of the WHO criteria to populations that were not used in the original data development including: men, non-Caucasian populations, premenopausal women, children, patients with glucocorticoid-induced bone loss, patients with renal osteodystrophy, etc.
2. The assumption that the WHO criteria, which are diagnostic thresholds, are also intervention thresholds. It was never the intent of the WHO working group that their diagnostic criteria be used as thresholds for treatment intervention.

The ISCD held Position Development Conferences (PDC) to address many of the issues facing clinicians related to the application of bone density measurements. The process of the ISCD-PDC and the results of that process have been published in *The Journal of Clinical Densitometry* (JCD) and other peer-reviewed journals [29, 30].

Even though the WHO population used for the criteria development was Caucasian and female, it is felt that the WHO criteria can be used for the diagnosis of osteoporosis in men 50 years of age and older. Justification for this *recommendation is based on observations that men and* women fracture at similar absolute femoral neck BMD (Fig. 6) [26]. It is still recommended that T-scores for men be calculated from a male young-normal reference database. Justification for this is that even though the similar hip fracture risk in men as in women may be seen when the T-score is calculated from a female NHANES III reference population database, the prevalence of osteoporosis is underestimated when applying a T-score in men from a female as opposed to a male reference database [31, 32].

While there is increasing longitudinal data examining the relationship of BMD to fracture risk in men, there is very little data defining the relationship of low BMD to fracture risk with the intent of applying WHO diagnostic criteria to non-Caucasian populations. The ISCD has suggested [32, 33]:

- The use of a uniform Caucasian (non-race adjusted) female normative database for women of all ethnic groups
- The use of a uniform Caucasian (non-race adjusted) male normative database for men of all ethnic groups

Even though the central DXA machines have multiethnic reference population databases for calculation of T-scores or Z-scores (age-matched), there is paucity of data on the relationships between ethnic-specific derived T-scores and life-time fracture risk. In addition, at least for the USA population, there is only one head-to-head multiethnic fracture study that has suggested that the relative risk for fractures over 1 year was similar in Caucasians, African

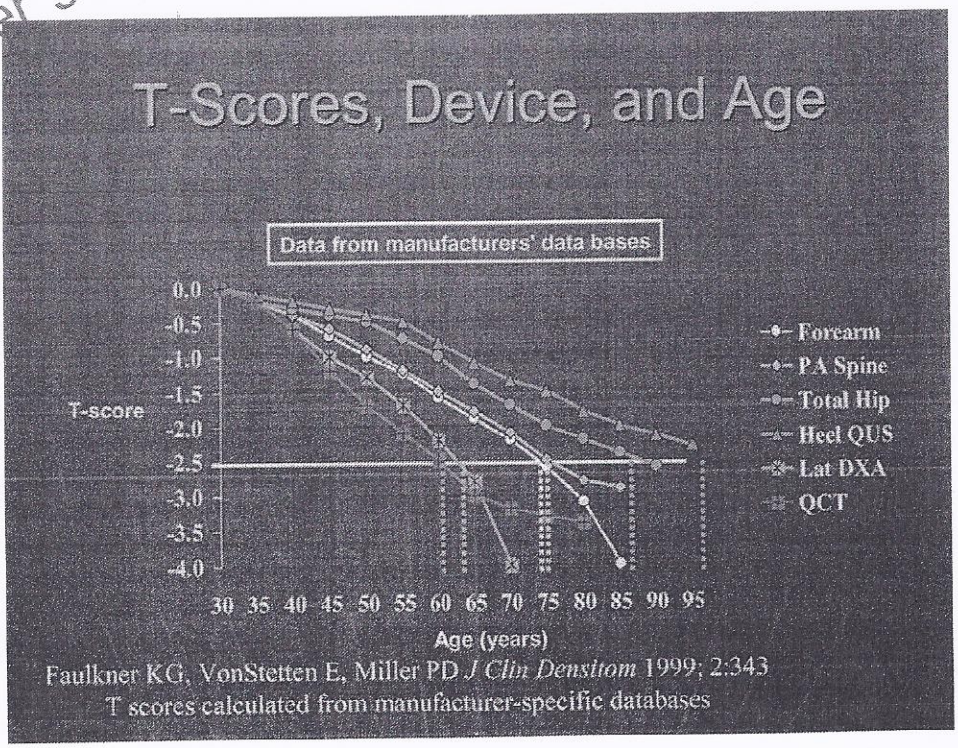

Fig. 2 Age-related decline in mean Caucasian female T-scores for different BMD technologies based on manufacturer reference ranges. The hip DXA reference data are from the NHANES study as implemented on all DXA devices from all manufacturers. The DXA normative data for the PA spine (L1–L4), lateral spine (L2–L4), and forearm (one-third region) were obtained from the Hologic QDR-4500 densitometer. Heel normative data were taken from the estimated BMD for the Hologic Sahara ultrasound unit. Spine QCTs are those used by the Image Analysis reference system. (—○—), heel; (—◇—), total hip; (—●—), PA spine; (—△—), forearm; (—✱—), lateral spine; (—✚—), QCT spine. Originally published in Faulkner et al. [8]

Table 2 *Indications for bone mineral density (BMD) testing*

1. Women aged 65 and older
2. Postmenopausal women under age 65 with risk factors
3. Men aged 70 and older
4. Adults with fragility fracture
5. Adults with a disease or condition associated with low bone mass or bone loss
6. Adults taking medications associated with low bone mass or bone loss
7. Anyone being considered for pharmacologic therapy
8. Anyone being treated, to monitor treatment effect
9. Anyone not receiving therapy in whom evidence of bone loss would lead to treatment

Adapted from The Writing Group for the ISCD Position Development Conference [30].

Americans, Hispanics, and Asian postmenopausal women when the T-scores were calculated from a Caucasian reference population [34] (Fig. 7). Absolute fracture rates were lower in Asians and African-Americans in the NORA study. Therefore, in many parts of the world where gene-pool mixing across multi-ethnic populations is common, Caucasian reference population databases may be considered for T-score calculation in all ethnic groups. In an ideal world, nation-specific and ethnic-specific reference population databases would be created and the nation-ethnic-specific T-scores would be linked to longitudinal fracture risk data. This would be an enormously prohibitive and expensive undertaking that might not convey substantial risk prediction benefit between multi-ethnic populations. What is Race?—has been the theme of many scientific analysis [35, 36]. While it appears throughout multiple studies that in some specific populations fracture risk is clearly lower (lower hip fracture risk in Asians and Blacks), there is also a high variability in hip fracture rates within geographic regions of the world even among Caucasians [37]. On the other hand, some specific types of fractures are not too dissimilar between multi-ethnic groups. For example, the prevalence of morphometric vertebral fractures as a function of age appears to be similar between Asians, Hispanics and Caucasians [38–42]. There is no simple resolution to this multi-ethnic-reference population database issue. As mentioned, until we have better answers from better data, a Caucasian reference database for all ethnicities seems reasonable, albeit imperfect, realizing that prevalence estimates for osteoporosis or osteopenia will differ from estimates obtained from ethnic-specific reference population databases vs ethnic-specific reference population databases due, in part, to the different SD of the mean BMD that is inherent in the T-score calculation.

2 The use of BMD for fracture risk assessment

While the T-score has (and will remain) an important "number" for the diagnosis of osteoporosis, it is clear from the preceding discussion that the impact of the T-score on patient risk assessment and management depends heavily

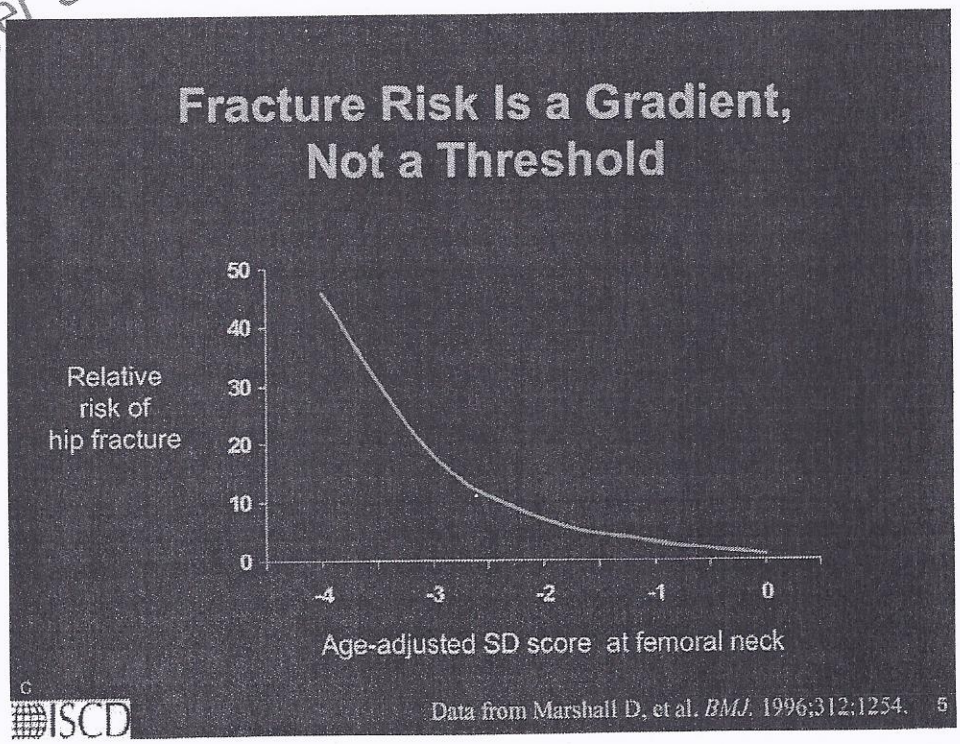

Fig. 3 The relative risk of hip fracture is a gradient, rather than a threshold. Adapted from data reported in Marshall et al. [23]

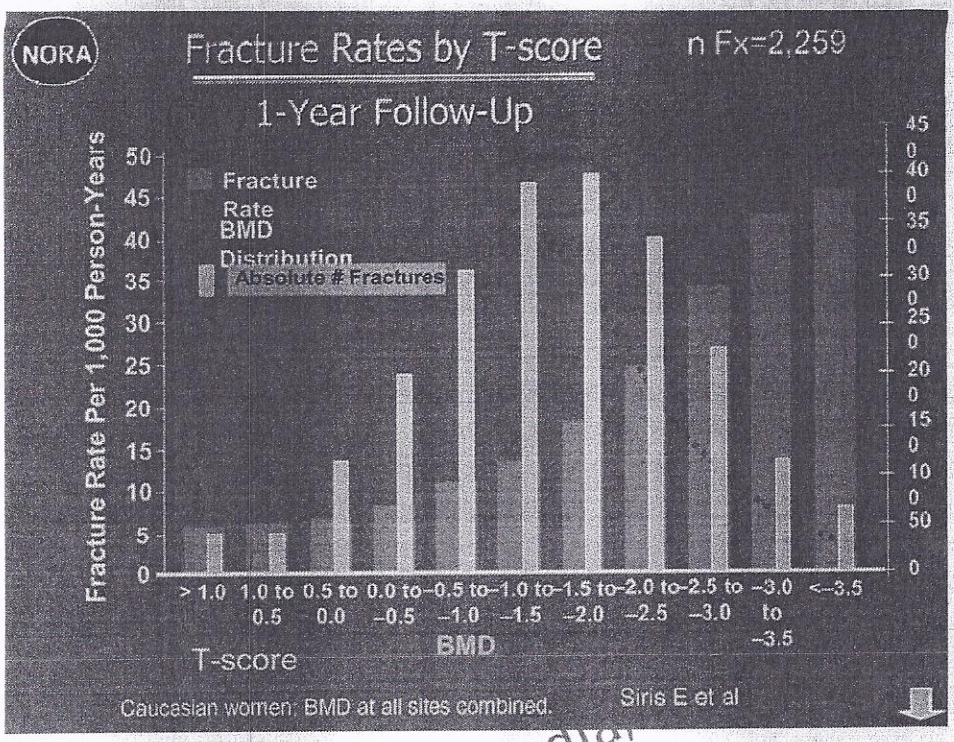

Fig. 4 Bone mineral density, osteoporotic fracture rate and number of women with fractures. Originally published in Siris et al. [25]

on how the T-score is interpreted [15, 16]. A low T-score has very different implications at age 50 years vs age 80 years—hence in isolation, a "T-score is not a T-score is not a T-score." The combination of a T-score and additional risk factors for fracture provides a more refined quantitative assessment of fracture risk than can be obtained by a low BMD alone. It is important to stress, however, that the diagnosis of osteoporosis can be made based on the presence of a fragility (low-trauma) fracture, regardless of the level of the T-score, which is the manner in which osteoporosis was diagnosed before the WHO criteria were developed. Fractures that are predictive of a higher risk for

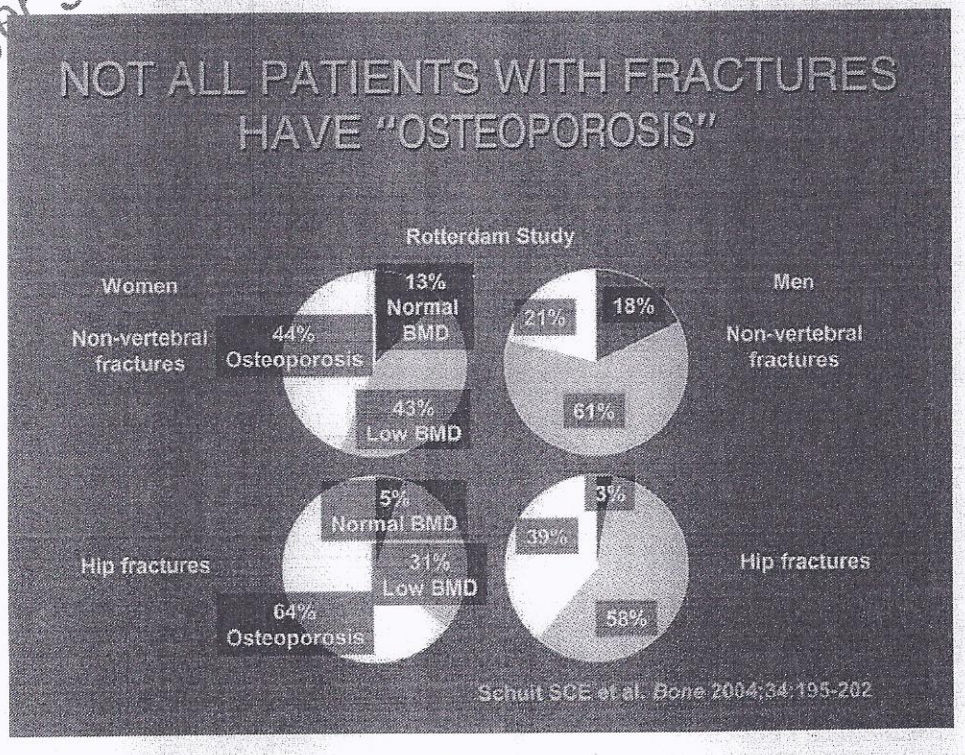

Fig. 5 Most non-vertebral fractures occur in men and women who do not have osteoporosis by World Health Organization DXA criteria measured at the hip. Originally published in Schuit et al. [27]

future fracture in population studies as well as placebo arms of pharmacological clinical trials are: vertebral fractures (VCF), hip fractures, wrist and forearm fractures, humeral and shoulder fractures, and rib fractures [43–51]. Fragility fractures at these sites are predictive of future fracture risk independent of the BMD. Forearm fractures, previously shown to be predictive of a high risk for other non-forearm fractures (Table 3) [51], have also recently been shown to also predict a high risk for other fractures in the large longitudinal NORA database. In NORA, all (global) fragility fractures were captured after the age of 45 years before as well as over the first 1–3 years after entry into NORA. There were 8,554 prior wrist fractures [52] In these postmenopausal women a prior wrist fractures was associated with a large increase in a brief period of time of another fracture, even at distant skeletal sites (e.g., hip). Just why a prior fragility fracture conveys a high risk for fracture at other skeletal sites is not clear, except to suggest that a fracture is symbolic of systemic skeletal fragility.

It was recognized in 1991 that the presence of a morphometric VCF increased the risk of future fractures of the vertebrae independent of the baseline BMD, and the presence of an existing VCF in combination with low BMD increased the future fracture risk far more that the risk predicted by either a VCF or low BMD alone [2, 53] (Fig. 1).

Low BMD as measured by central or peripheral DXA, peripheral ultrasound, or spine QCT is predictive of an increased risk for fractures at any other skeletal site [23, 54–63].

In addition, from individual longitudinal studies, including population studies, and from meta-analysis, all of these BMD measuring devices predict an increased risk of fracture in postmenopausal women or elderly men with an overlapping relative risk (RR) predictability: risk increases ~2 times for each 1.0 SD reduction in BMD calculated from T-scores, or the variance from the mean of an aged-matched population [23].

However, fracture risk discrimination is quantified by the magnitude of the RR, e.g., the larger the value of RR, the more effective measurements are at identifying patients at increased risk of fracture. It has been suggested that the reason that all BMD measurements are capable of predicting similar RR for fracture, even at skeletal sites other than the measured site, is due to the high correlation coefficients among BMD technologies (r=0.55–0.65) [64]. If, however, there are unrecognized deviations from the published correlation coefficients among BMD technologies, then there may be room for improvement in fracture prediction. In part, fracture risk prediction can be enhanced by incorporating additional risk factors into the assessment of fracture risk. The validation of how additional risk factors should be added to BMD to enhance risk prediction is important since the current DXA reports may be misleading in their subjective pronouncements of fracture risk.

It has been recognized since the forearm DXA studies of Hui, et al. that fracture risk is dependent upon the age of the patient [65] (Fig. 8). Any given patient's risk for fracture increases as age increases even at the same BMD or T-score level [65, 66]. Thus, DXA measurements capture an important, albeit fraction of the fracture risk. Understanding this fundamental point is pivotal to the proper interpretation of BMD values. The reason why risk is greater as age increases is not completely understood but the higher risk for falls in the elderly may account for a portion of this age-related greater risk for fracture [67]. Older bone has less strength to resist fracture than younger bone at the same BMD or T-score, and investigators dedicated to measuring bone quality are refining our understanding of these issues [68–71]. It is important to point out, however, that even though the absolute risk for fragility fracture increases at the same level of BMD or T-score as age increases [72], fractures at both hip and non-hip skeletal sites are not infrequent in the younger (50–64 years) postmenopausal population. In the NORA study nearly (37%) of all fractures occurred in this younger untreated postmenopausal group, and was lower the lower the T-score value [73] (Table 4).

As previously mentioned, prior fracture in the postmenopausal population is an independent predictor of future fracture risk. Furthermore, combining a prevalent fracture (even asymptomatic vertebral fracture) and low BMD translates into a much greater risk for future fracture than what would be predicted by low BMD or prior fracture alone [2]. In 1993, data showed the interaction of risk factors captured in the Study of Osteoporotic Fractures (SOF) with low BMD to enhance fracture risk prediction for hip fractures [74] (Fig. 9). More recently, data from multiple population studies have documented the strong association between the presence of non-vertebral or non-hip fractures and fragility fractures of other skeletal sites including shoulder, wrist and rib fractures [10, 37, 53, 75]. Therefore, in the elderly population, any fragility fracture is symbolic of systemic skeletal fragility.

Clinicians should, therefore, incorporate BMD, age, and prior fracture in their assessment of fracture risk and patient management. Recent software upgrades in central DXA machines may use these three risk factors to calculate fracture risk. Broad implementation of standardized DXA reports can only be realized when the independent risk factors for fragility fractures in the postmenopausal population are validated and endorsed at an international level.

The WHO absolute risk project, is the large project assessing the long-term (10 year) risk for all fragility fractures as a function of validated risk factors from large international studies [66]. This work, spearheaded by Professor John Kanis [76], is still in progress and will require review and comment by the WHO per se before final publication and ultimate implementation. Based on

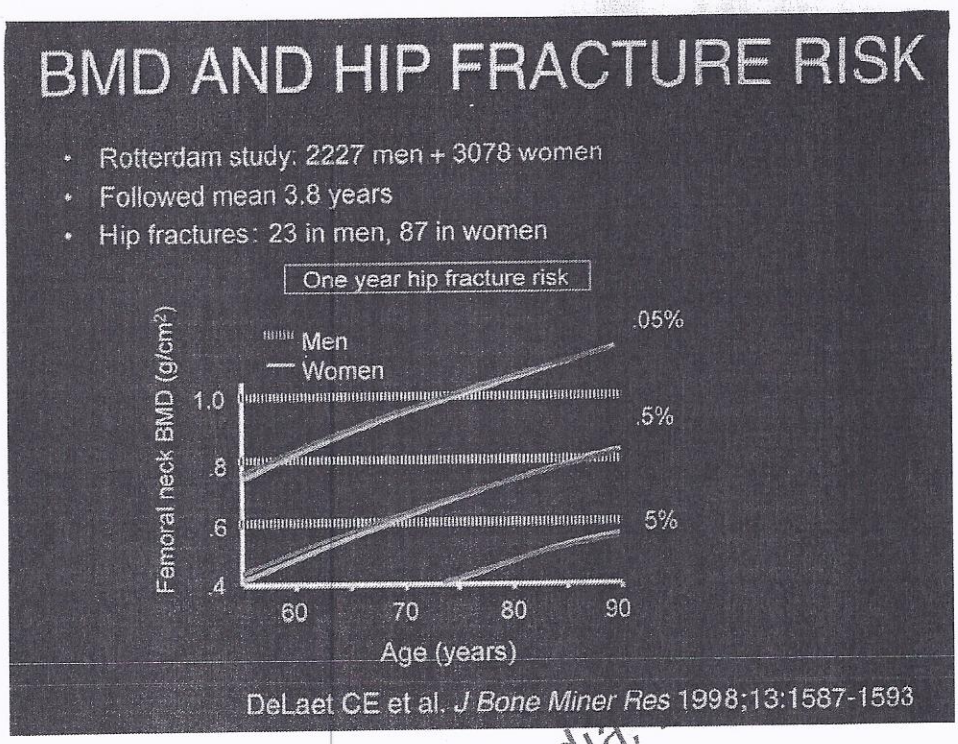

Fig. 6 One-year hip fracture risk by age and bone mineral density from the Rotterdam Study. Women (▮▮▮▮▮▮); men (▮▮▮▮▮▮). Adapted from data presented in De Laet et al. [26]

data that have already been presented at many scientific meetings, there are eight independent validated risk factors for fracture risk. Those that may be included in the implementation of standardized DXA reports are BMD, prior fragility fracture, age, and family history, since beyond four or five risk factors, the absolute risk level increases only slightly. The combined risk factor analysis refines risk stratification. When implemented, it is hoped that absolute risk prediction calculation will facilitate intervention decisions for the postmenopausal population based on risk beyond a T-score value alone. Risk stratification has been shown in previous analysis, however they are either based on restricted population studies or use peripheral BMD technologies for risk assessment [77, 78]. The WHO absolute risk study will link absolute risk for all fractures, calculated from validated population studies

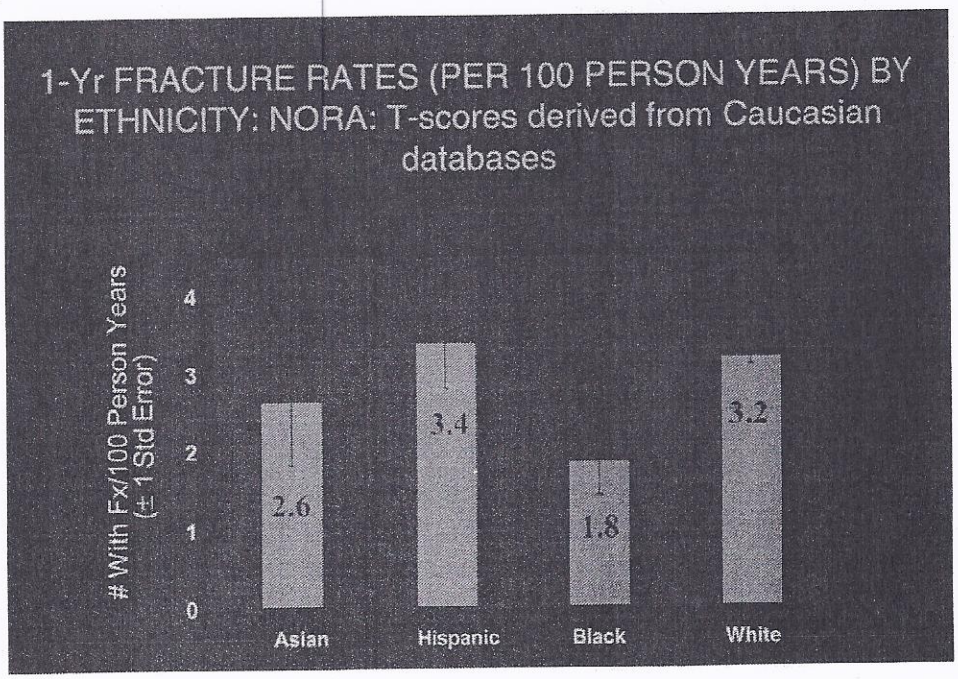

Fig. 7 One-year fracture rates expressed per 100 person years in Asian, Hispanic, Black and White ethnic groups from the NORA Study. Adapted from data presented in Barret-Conner et al. [34]

Table 3 Prior fracture as a predictor of fracture risk

Prior fracture relative	Risk of future fractures		
	Wrist	Vertebra	Hip
Wrist	3.3	1.7	1.9
Vertebra	1.4	4.4	2.3
Hip	NA	2.5	2.3

Originally published in Klotzbuecher et al. [51].

representing >90,000 postmenopausal women, to treatment intervention based on disutility costs of hip fracture using the current costs of drugs registered for the treatment of PMO.

It is obvious that the government reimbursement plan will differ nation to nation by the GDP of a given nation. The WHO project does not include other risk factors that clinicians might reasonably use in counseling patients: non-clinical (morphometric) vertebral fractures, bone turnover markers, hip axis length, hip structural analysis and other risk factors that might become identified in smaller, less well validated multi-nation population studies [46, 79–86]. Morphometric vertebral fractures, however, will be acknowledged by the NOF clinical implementation of the WHO absolute risk analysis as being a strong risk factor for future fracture. In addition, the WHO absolute risk model will provide broad generalizations which will focus on intervention strategies, but it will not eliminate individual clinician decisions. Nevertheless, the WHO risk project will take the field of osteoporosis to a level comparable to the cardiovascular field regarding intervention decisions. In addition, the WHO absolute risk assessment may advocate treatment of women whose lower T-scores or younger age might otherwise not have received treatment [66] (Fig. 10).

Table 4 In the National Osteoporosis Risk Assessment (NORA) study approximately one-third of all fractures and one-fifth of hip fractures occurred in women less than 65 years of age

Age	50–64	65+
Osteoporotic fracture		
Number of fractures	905	1,535
Fracture rate (95% CI)	8.4 (7.9, 9.0)	16.5 (15.6, 17.3)
Percent of fractures	37%	63%
Hip fractures		
Number of fractures	86	354
Fracture rate (95% CI)	0.8 (0.6, 1.0)	3.8 (3.4, 4.2)
Percent of fractures	20%	80%

Adapted from data from Siris et al. [73].

The WHO selected absolute risk rather than relative risk even though both calculations of risk have value. The power of any given BMD measurement device to predict risk is based on its ability to predict RR. Yet, RR does not incorporate other risk factors, it is the ratio of the absolute risk for the disease event in a target population to the absolute risk in a population not at risk for the disease event (BMD, smoking, etc). Absolute risk incorporates the discovered cumulative risk factors into the prediction of

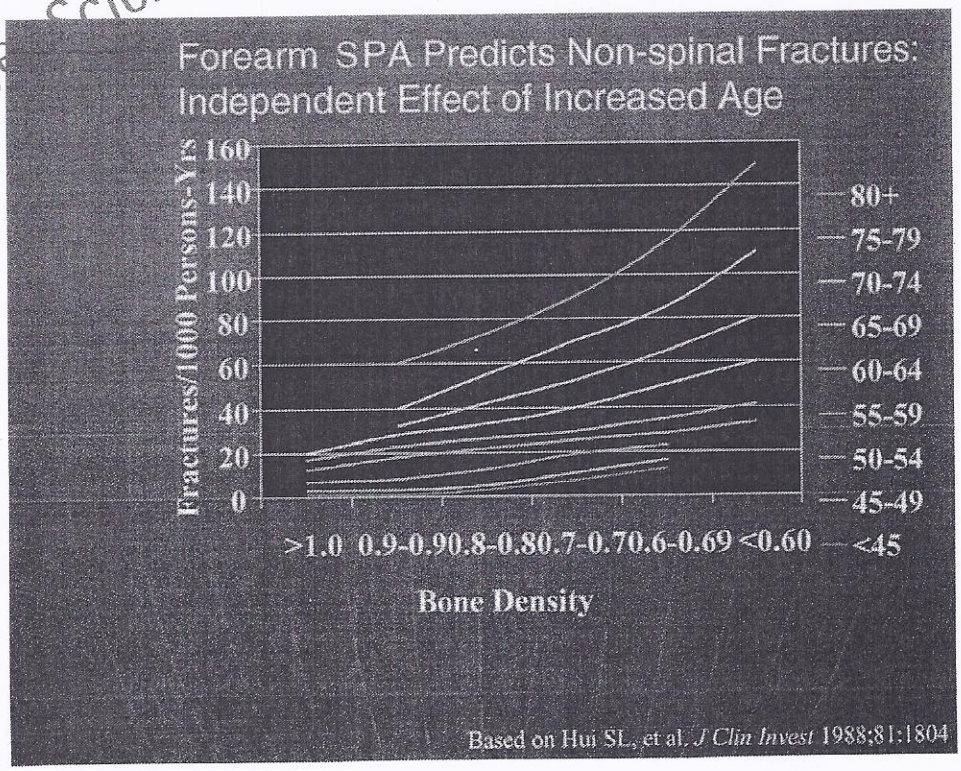

Fig. 8 The relationship between increasing age, bone mineral density measured at the forearm by single photon absorptiometry (SPA) and non-spinal fractures in Caucasian women followed for 6.5 years. Adapted from Hui et al. [65]

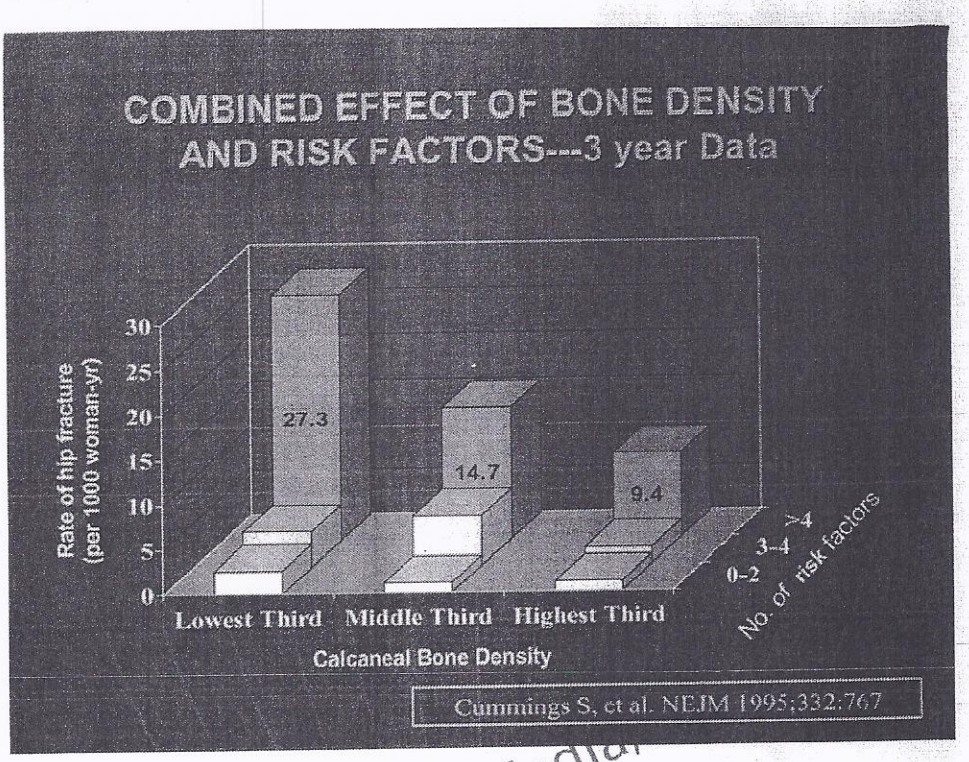

Fig. 9 The combined effect of bone mineral density (BMD) and other risk factors on the rate of hip fracture per 1,000 person years. Adapted from Cummings et al [74]

the risk for fractures over a given period of time [64]. As shown in Table 3, the RR risk for fracture per SD reduction in BMD is constant over age, which is incorrect. As other risk factors are included in this calculation, the absolute risk will increase with age.

3 Risk assessed by vertebral fracture assessment (VFA)

DXA is now a recognized technology for the identification of vertebral fractures. The presence of vertebral fractures, even if they are asymptomatic, is predictive of the risk for

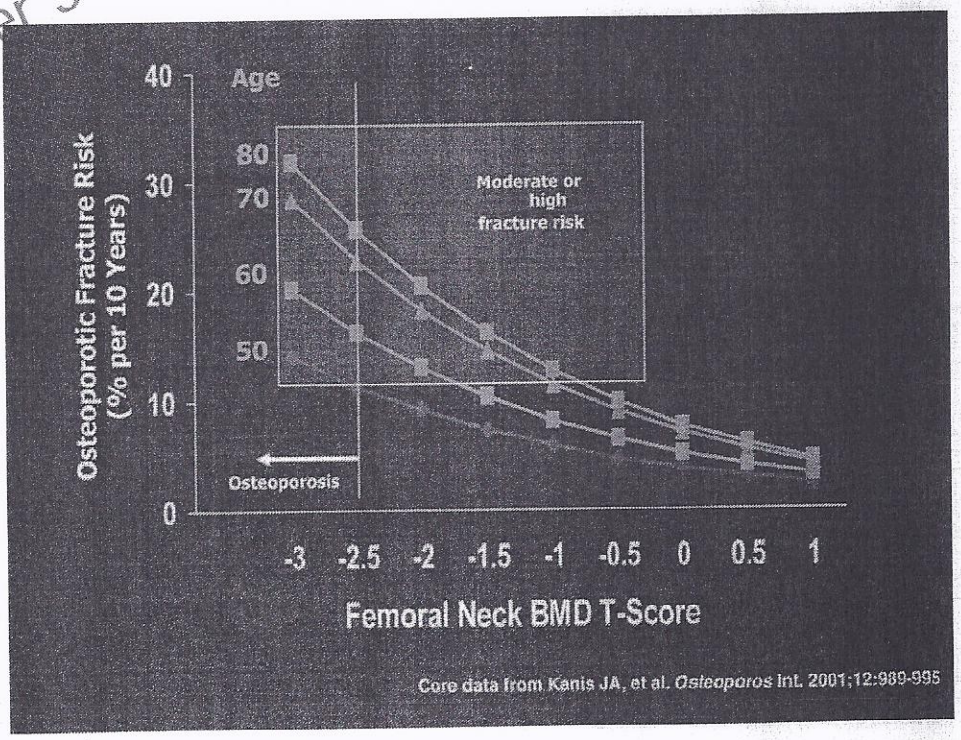

Fig. 10 Graphic depiction of the World Health Organization absolute risk analysis based on age and femoral neck BMD T-score. Adapted from data presented in Kanis et al. [66]

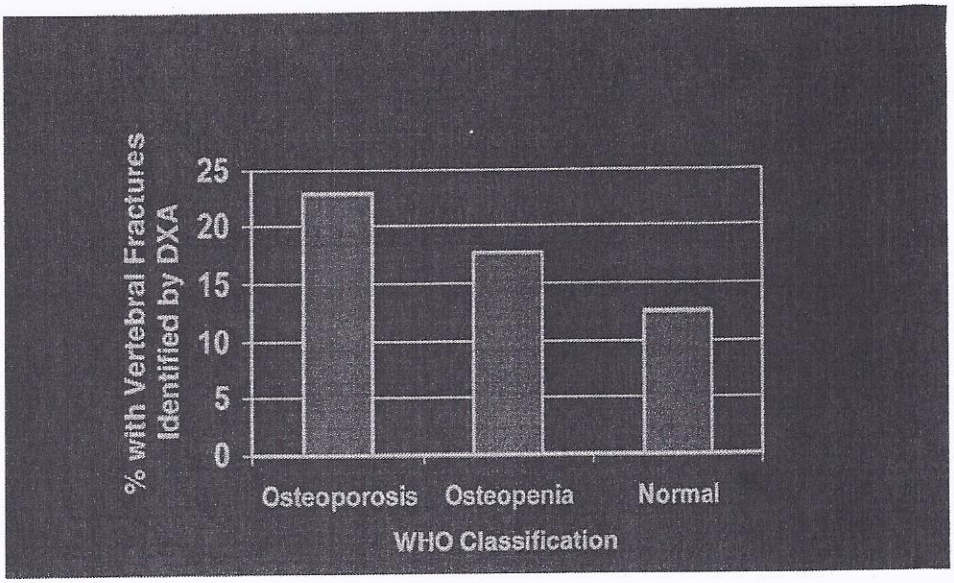

Fig. 11 Classification by bone mineral density alone misses women with vertebral fractures. Greenspan et al. [87]

future (incident) vertebral fractures and non-vertebral fractures, independent of baseline BMD or T-score. In addition, many patients without WHO defined osteoporosis have prevalent vertebral fractures (Fig. 11) [87]. The majority of prevalent vertebral fractures are not recognized in postmenopausal women and elderly men. Population studies from the USA, Europe, Mexico, and Asia all suggest that vertebral fracture prevalence is similar across these ethnic groups and may be as high as 60–65% by the age of 65 years [38–42]. This suggests that osteoporosis is markedly under-diagnosed and that future fracture risk is markedly under-estimated. Professor Harry Genant [88] has provided clinicians with a semi-quantitative method for the identification of prevalent, as well as, incident vertebral clinical fracture (VCF) utilizing either plain radiography or DXA-based VFA. The VFA technology for prevalent VCF detection by DXA has progressed to the point that it is becoming a standard of care in the risk assessment of the postmenopausal population. The ISCD has provided guidelines for VFA determinations [89]. Table 5 outlines the ISCD indications for VFA by DXA.

If clinicians simply measure the height of their postmenopausal patients and perform a VFA assessment in those who have lost more than 1.5 in from their historical height, there is evidence that a large proportion of vertebral fractures will be detected [90].

There is data to suggest that all "grades" of prevalent vertebral fractures are predictive of future fracture and that this risk is increased within 12 months of the detection—even though the physician may not know when the prevalent vertebral fracture occurred [46, 81, 91, 92]. The higher the grade (severity) of the existing vertebral fracture, or the more vertebral fractures present (one, two or three), the greater the risk for future fractures (Figs. 12 and 13) [81]. Furthermore, since these vertebral fractures, even those that are asymptomatic, are associated with a high risk of fractures even at non-vertebral sites; and, are also associated with a higher morbidity and mortality as compared to age-matched patients without vertebral fractures, the detection of VCF will not only establish a diagnosis of osteoporosis regardless of the prevailing T-score [87] but also identify a high risk for fracture group that merits treatment.

Thus, the advancements in DXA technology [93, 94] that allow physicians to identify a prevalent VCF at the point of care when the BMD is done by DXA for diagnosis, risk assessment, or monitoring has improved the management and assessment of the osteoporotic patient.

4 Conclusions

A BMD measurement by DXA is the most important clinical tool to allow the field of osteoporosis to move from theory to practical application. Proper interpretation of

Table 5 Indications for vertebral fracture assessment (VFA)

1. Consider VFA when the results may influence clinical management
2. When BMD measurement is indicated, performance of VFA should be considered in clinical situations that may be associated with vertebral fractures.

Examples include:

Documented height loss greater than 2 cm (0.75 in)

Historical height loss greater than 4 cm (1.5 in) since young adulthood

3. History of fracture after age 50
4. Commitment to long-term oral or parenteral glucocorticoid therapy
5. History and/or findings suggestive of vertebral fracture not documented by prior radiologic study

Originally published in Vokes et al. [89].

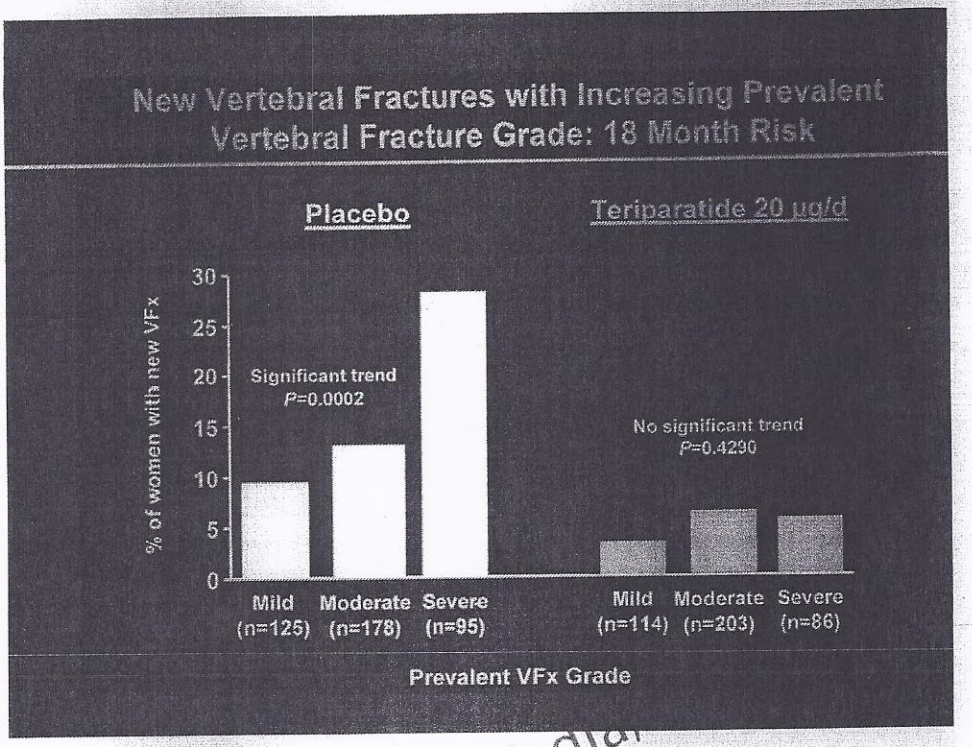

Fig. 12 Increased number of new vertebral fractures in subjects with mild, moderate and severe prevalent vertebral fractures. Originally published in Gallagher et al. [81]

BMD results, including the proper use of T-scores, fracture risk assessment, and monitoring BMD over time provides the clinician with the best clinical information to use in the management of the osteoporotic patient. Central DXA utilization requires strict quality control of the measurements performed by DXA technologists and well-educated physicians who interpret the results [95–98]. The trust a clinician and patient place on DXA measurements lies in the appropriate interpretation of the result. The implementation of the validated WHO absolute fracture risk project should facilitate decision making for management of the patient with postmenopausal osteoporosis.

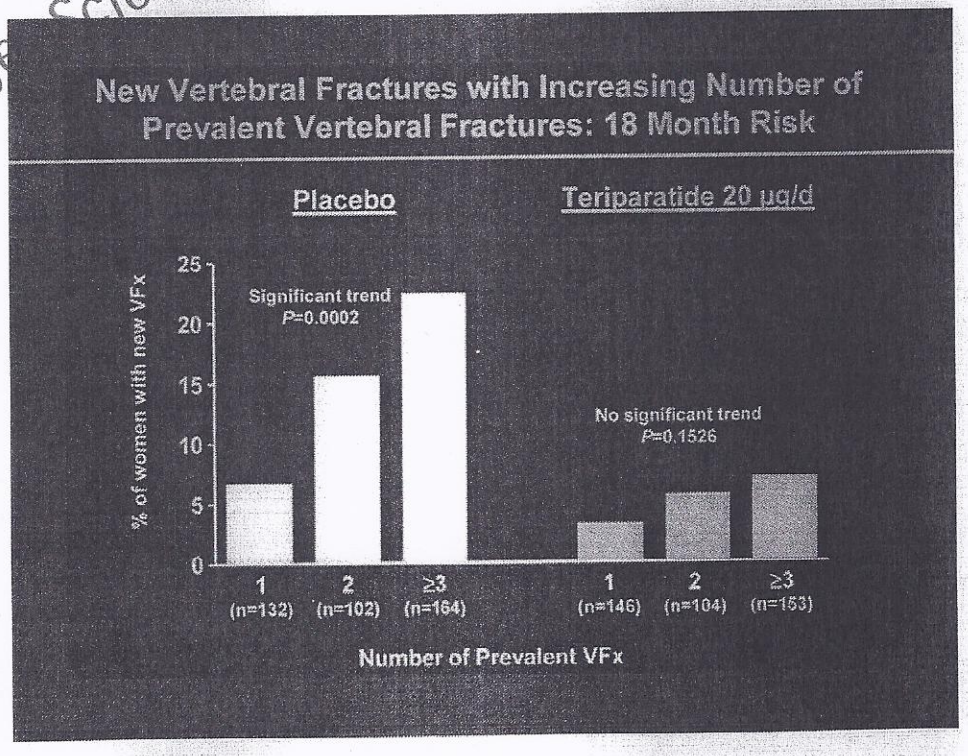

Fig. 13 Increased number of new vertebral fractures in subject with one, two, and more than three prevalent vertebral fractures. Originally published in Gallagher et al. [81]