

Osteoporosis Risk Factor Assessment and Bone Densitometry—Current Status and Future Trends

L K H Koh,**FAMS, M Med (Int Med), MRCP*, D C E Ng,***FAMS, MRCP*

Abstract

Introduction: Osteoporosis and fragility fractures are problems which will increase in significance as the population of the elderly in many countries increases. The availability of bone mineral density (BMD) measurements, which can define osteoporosis, allows the implementation of effective therapeutic interventions to those at risk for fractures before they occur. Because of the increasing at-risk population and the relatively high cost of these measurements and interventions, a case-finding strategy to detecting osteoporosis has been widely recommended. This review highlights the approach to detecting and diagnosing osteoporosis. **Methods:** A non-systematic review of English-language literature on the diagnosis and assessment of osteoporosis was conducted. **Results:** Many risk factors have been found to be associated with osteoporosis and fractures. These risk factors may be utilised for case finding in deciding who should be evaluated for osteoporosis. Clinical self-assessment tools have been developed to identify women likely to have low BMD who might be recommended for BMD. Several techniques are available for BMD measurement, but the technique of choice for the diagnosis of osteoporosis is dual-energy X-ray absorptiometry (DXA) measured at the hip. BMD thresholds have been widely used to guide osteoporosis treatment. However, recent research has been directed at using risk factor assessment and self-assessment tools to derive medium-term fracture risk as a guide to therapeutic intervention. **Conclusions:** Proper selection of individuals for evaluation and treatment for osteoporosis would include risk factor assessment and appropriate BMD measurement to determine the risk of fracture and the need for intervention.

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Introduction

Osteoporosis affects predominantly elderly women; although younger women and men may also be affected. Demographically, the number and proportion of the elderly (aged 65 years and above) in many countries is increasing rapidly, and the problem of osteoporosis will increase concomitantly. In 1990, only 6% of the population in Singapore was above the age of 65, but by 2030, this figure is projected to rise to 19%.¹ The most serious end-point of osteoporosis is fragility fracture. Increases in hip fracture rates have been documented in many countries² including Singapore,³ and worldwide projections predict further increases in hip fracture incidence to epidemic proportions.^{4,5} Vertebral fracture rates among Asian populations are already as high as in Caucasian populations.^{6,7} An increasing awareness about the problem of osteoporosis and the development of effective treatments are likely to increase the demand for proper diagnosis and management of patients with osteoporosis. In recent years, several

developments have occurred which have impacted on our approach in addressing this problem.

Definition of Osteoporosis

An International Consensus Development Conference defined osteoporosis as a 'progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture'.⁸ This conceptual definition implies that bone mass or density is an important component and a measure of the risk of fracture, and that other abnormalities in the skeleton contribute to skeletal fragility. This definition, however, does not consider other non-skeletal factors which contribute to fracture risk.

A Working Group of the World Health Organization (WHO) operationally defined osteoporosis as a value for bone mineral density (BMD) that was 2.5 standard deviations or more below the mean peak value in young

* Consultant

Department of Endocrinology

** Associate Consultant

Department of Nuclear Medicine

Singapore General Hospital

Address for Reprints: Dr Leonard Koh, Department of Endocrinology, Singapore General Hospital, Outram Road, Singapore 169608.

adults, and severe or established osteoporosis as the same threshold in the presence of one or more fragility fractures.⁹ This definition has been widely used in studying the epidemiology of osteoporosis and in clinical trials. In patient care, the diagnostic threshold has often been utilised as a threshold for treatment, although this was not the original intention. This definition is limited by its inability to assess the importance of other determinants of bone strength, to take into account the effect of other factors at any given BMD on fracture risk, and to specify the technique or site for BMD measurement. Despite these limitations, in the absence of fragility fractures, BMD remains the method for diagnosing osteoporosis.

Diagnosis of Osteoporosis

Bone Mineral Density

BMD is a measurement which gives an idea of fracture risk. BMD results are reported as T-scores (comparing the individual's bone density with the mean found in young healthy adults) and Z-scores (comparing with the mean level in people of the same age).^{9,10} The T-score is used in the WHO criteria to define the threshold below which osteoporosis is diagnosed, while the Z-score estimates the relative risk of fracture.

Prospective studies have shown that the risk of fracture increases progressively with decreasing BMD. Using absorptiometric techniques, the risk of fracture increases approximately two-fold for each standard deviation decrease in BMD.¹¹ The gradient of risk varies according to the measurement site and technique used.

Non-invasive techniques available in Singapore for measuring BMD include dual-energy X-ray absorptiometry (DXA) of hip and spine, single-energy X-ray absorptiometry (SXA) of forearm or heel, quantitative ultrasound (QUS) of the heel, tibia or multiple sites, and quantitative computed tomography (QCT) scans of the vertebra. Other methods include single photon and dual photon absorptiometry (SPA and DPA, respectively) which were used in the past, peripheral QCT (pQCT) of the forearm and radiographic absorptiometry (RA) of the hand.

DXA is based on the use of x-rays of 2 different energies which can be normalised to each other in order to remove the contribution to attenuation by soft tissues, allowing the attenuation due to bone alone to be measured. Because DXA can correct for soft tissue attenuation, DXA can be used to measure BMD at the hip and lumbar spine. The precision of DXA devices is relatively good and of the order of 1% to 3%, and the accuracy is of the order of 4% to 10%.¹² Each DXA measurement typically takes 10 to 15 minutes.

QUS is a relatively newer clinical technique although primary research into this modality dates back at least 2

decades. This technique measures the velocity and broadband attenuation of high frequency sound waves which are scattered and absorbed by cortical and cancellous bone, as they pass through accessible bones such as the tibia or calcaneum.¹² A secondary index called the stiffness index can be calculated from these measurements. The precision of this technique is reported to be in the order of 3% to 8%,¹³ but the accuracy remains undetermined. The advantages of this technique are the absence of ionizing radiation and portability of the devices. QUS has been shown to correlate fairly well with DXA,¹³ and to predict fracture risk independently of DXA.^{14,15}

QCT provides a volumetric BMD (g/cm³), unlike DXA which provides an areal density (g/cm²) and it can discriminate between cortical and cancellous bone. The precision is reported to be in the order of 2% to 4% while the accuracy is in the order of 5% to 15%.¹² The major drawback is its relatively high radiation exposure.¹⁶

The use of quantitative magnetic resonance (QMR) and magnetic resonance microscopy (μMR) as tools for the assessment of osteoporosis are being explored. Although MR imaging may not measure bone density directly, it may provide information on the trabecular microstructure of bone.^{12,17} Thus far, the precision of QMR appears poorer relative to DXA and QUS.¹⁸

There has been poor concordance of BMD measurements at different sites with the same techniques, and between different techniques. All current BMD methodologies are limited by differing degrees of errors of accuracy and precision.¹⁹ Factors such as the measurement of areal rather than volumetric bone density, soft tissue density, fat distribution, biologic variability in bone structure, bone composition, bone loss rates, poor correlation of bone density between skeletal sites and variance of measurements in the population being examined contribute to these errors. As a result, T-scores at different sites and with different techniques yield different information on fracture risk. T-scores therefore cannot be used interchangeably between sites and techniques.

Because of the inherent misclassification errors in using different sites and techniques, there has been a need for a 'gold standard' for the purposes of diagnosing osteoporosis. Hip measurements using DXA seem to fulfill this role because they have the highest predictive value for hip fractures, and are as good or better than other measurement techniques at predicting other osteoporotic fractures. Moreover, they have been validated in many prospective studies. T-scores should therefore be reserved for measurements at this site,¹⁹ conventionally using the unfractured or non-dominant hip. Among the different measurement sites, the lumbar spine usually shows the greatest BMD response to treatment, and is the preferred

site for monitoring therapeutic response. However in the elderly, spurious increases in spine measurement by conditions such as osteoarthritis, fractures and calcification of the aorta may occur, in which case, monitoring is best done at the hip site.

The other techniques may be reasonable if incorporated with the use of risk factors in comprehensive fracture risk assessment to aid in directing interventions to those at high risk. Since practically all recent intervention trials on osteoporosis have reported exclusively on DXA as the sole technique for measuring BMD,²⁰⁻²³ there is limited data and experience on the use of other techniques in monitoring response to therapy.

Attempts have been made to standardise the diagnostic threshold between different BMD techniques so that they may be interchangeable. An approach might be to equalise the apparent prevalence of osteoporosis at the age of 65 years, giving an identical estimate of the prevalence of osteoporosis at that age.¹⁹ However, because the rates of bone loss at different sites with different techniques differ, measurements at the age of 50 and 80 years would either underestimate or overestimate the risk of osteoporosis significantly.

Another issue which has arisen is that data for the development of the diagnostic thresholds for osteoporosis were derived from studies in postmenopausal Caucasian women. The applicability of these same thresholds to Asian subjects remains to be determined since hip fracture risk remains generally lower among Asians compared to Caucasians,³ despite having lower BMD.²⁴ As the diagnostic thresholds were based on the distribution of BMD in those populations, it would be reasonable for Asian reference databases to be used for deriving T-scores.²⁵ Ethnic group-specific databases should also probably be developed, as ethnic differences in hip fracture rates have been demonstrated in Singapore.³

The relationship between BMD and relative risk of hip fracture appears similar in men and women, although the data is rather scanty.²⁶ There is some controversy with regard to the diagnostic threshold for osteoporosis in men, for which values derived from both female and male populations have been used. In men, the risk of fracture is substantially lower for a bone mineral measurement within the male range, and in order to yield the same risk as in women, a more stringent criterion is required. The same absolute BMD value in men which corresponds to the female femoral neck T-score of 2.5 SD or more below the reference range for young women gives approximately the same absolute risk of vertebral and of hip fracture in men, and the use of this value has been recommended as the threshold for diagnosing osteoporosis in men,¹⁹ although this has not universally accepted.²⁷ It

would be necessary to obtain this value from the centre providing the BMD result since the value is specific to each measurement device.

Biochemical Markers of Bone Turnover

Over the last 20 years or so, there has been interest in the use of biochemical markers of bone turnover in the evaluation of osteoporosis. These markers are chemical substances released from bone and collagen-containing tissue which reflect the dynamic processes of skeletal biology such as bone formation and resorption. Examples of bone formation markers are serum bone alkaline phosphatase (bone ALP) and serum osteocalcin (OC), and bone resorption markers are urinary and serum collagen type I C-terminal telopeptide (CTX) and N-terminal telopeptide (NTX).

In the context of osteoporosis, the main potential uses of these markers are in prediction of the risk of fracture, prediction of the rate of bone loss and monitoring of the efficacy of anti-resorptive therapy.²⁸ There is currently no role for biochemical markers in the diagnosis of osteoporosis.

Various studies demonstrate that bone turnover markers are able to predict the risk of fracture, even after correcting for the contribution from measurements of BMD,²⁹ and may actually improve prediction if used in combination with BMD.³⁰ There have been recent suggestions to incorporate bone turnover markers in deriving risk estimates for fracture to guide decisions in therapy.^{28,31}

Resorption markers reflect the rate of bone loss and may identify a group of “fast bone losers” who have an accelerated rate of bone loss of greater than 3% per year as measured by standard BMD. However, the clinical significance of these studies has been limited by the relatively short duration of most studies and the imprecision of most biomarker assays.²⁸

Risk Factors

The non-invasive measurement of BMD has made it possible to diagnose osteoporosis before the main health outcome of fragility fractures occur. Effective agents for the treatment of osteoporosis are constantly being developed. However, BMD measurements and osteoporosis treatments are costly. Although the definition of osteoporosis is based on BMD, it is not advisable to screen BMD in the whole population.¹⁰ The decision to test for BMD should be based on each individual's risk for osteoporosis in a ‘case-finding’ approach. Testing is also generally not indicated unless the results could influence a treatment decision.

In several large epidemiological studies,³²⁻³⁴ including some from Asia,^{35,36} many risk factors have been found to

TABLE I: RISK FACTORS FOR OSTEOPOROSIS AND FRACTURE

Risk factors for low bone mass and fracture:Non-modifiable

- Personal history of previous fracture as an adult
- History of fracture in a first-degree relative (especially maternal)
- Increasing age
- Low body weight
- Poor health and frailty from multiple illnesses

Potentially modifiable

- Current cigarette smoking
- Alcohol abuse (stronger data in men)
- Early natural or surgical menopause before age 45 years, or prolonged premenopausal amenorrhea lasting >1 year
- Drugs e.g. corticosteroids (equivalent to prednisolone >7.5 mg/day for more than 6 months), excess thyroxine, anticonvulsants
- Ongoing disease conditions e.g. hypogonadism, hyperthyroidism, hyperparathyroidism, Cushing syndrome, chronic obstructive airways disease, liver disease, malabsorption, chronic renal failure, rheumatoid arthritis, organ transplantation and anorexia nervosa
- Low calcium intake (<500 mg/day among Asians)
- Lack of regular physical activity

Other BMD-independent risk factors for fracture:

- Taller stature (>~1.6 m among Asian women, >~1.7 m among Asian men)
- One or more previous falls in the past year
- Strokes, poor balance, weak quadriceps muscle strength
- Impaired eyesight despite adequate correction
- Drugs e.g. sedatives, polypharmacy
- Environmental factors e.g. slippery floors, inadequate lighting

be associated with osteoporosis and fractures (Table I). These factors may affect the accrual of bone such that the genetically-programmed peak bone mass or optimal bone architecture may not be achieved. These factors may also result in enhanced bone loss over and above the natural decline in bone mass. Factors which increase the propensity to fall also appear to increase the risk of fracture.³⁷

Selecting Patients for BMD Measurement based on Risk Factors for Osteoporosis

The National Osteoporosis Foundation of the USA has recommended BMD testing in all individuals over 65 years of age, and for postmenopausal women under 65 years of age, case-finding by measuring BMD in individuals with common, accessible risk factors which were associated with hip fracture independent of bone density.¹⁰ These include a personal history of previous fracture as an adult, a history of fracture in a first-degree relative (especially maternal), body weight <57 kg or current cigarette smoking. It is not clear if these criteria are applicable to Asians.

Recently, a simple tool based on age and weight, the Osteoporosis Self-assessment Tool for Asians (OSTA), was developed for postmenopausal Asian women.³⁸ This tool was able to categorise women into high, moderate and low risk for finding osteoporosis on subsequent BMD

measurement. In the validation study, 61% of individuals in the high-risk category had osteoporosis as opposed to 15% in the moderate-risk category and 3% in the low-risk category. In the moderate-risk group, among women currently using oestrogen, 3% had osteoporosis. Because of the high prevalence of osteoporosis in the high-risk category, BMD measurement should be recommended for such women based solely on their age and weight. Among women in the moderate-risk category, risk factors for osteoporosis should be sought to decide who among these should have BMD assessment. In the low-risk category, BMD evaluation could be deferred unless risk factors were present since the prevalence of osteoporosis is low among women in this category.

The use of risk factors to optimise selection for BMD evaluation and treatment is preferred to blind treatment because not all patients with strong risk factors will have osteoporosis, and they may not benefit from treatment if selected only on the basis of risk factors without BMD evaluation.²³ Conversely, not all women with osteoporosis will have risk factors, and the use of age criteria or age-weight criteria attempts to increase the likelihood of capturing some of these women.

Selecting Patients for Treatment based on Risk Factors for Fracture

In addition to using risk factors in decision making for BMD, some of these risk factors represent secondary causes of osteoporosis. The secondary causes which are modifiable should be corrected, as there is evidence that bone loss and fracture risk may be reversed in some instances, such as with male and female hypogonadism, hyperparathyroidism and corticosteroid therapy. Other aspects of risk assessment in a clinic consultation might be directed at whether the individual might have conditions or situations which might mitigate for or against the use of particular drugs used in the treatment of osteoporosis.

Treatment should be considered in all patients with existing fragility fractures. In patients without fractures, the decision to treat an individual has usually been based on whether the individual's BMD falls below or approaches the diagnostic threshold. Some authors caution against this for several reasons: the same diagnostic threshold may not convey the same fracture risk between individuals in one country and another, or between individuals of different ages and with different risk factors, and does not address the cost-benefit of instituting treatment.¹⁹ However, as it has turned out in several intervention trials, it appears that only those with BMD in the osteoporotic range demonstrated significant fracture reduction,^{20,23} suggesting that the diagnostic threshold may actually be a useful measure by which benefits from therapy might be anticipated.

However, this approach might ignore the consideration that for many women identified as osteoporotic, the remaining lifetime fracture risk may be sufficiently low to render treatment inappropriate. Conversely, many women who do not have osteoporosis might have other risk factors and circumstances that would justify treatment.

In the management of osteoporosis, the risk of fracture is probably more important than the fulfillment of a diagnostic criterion. The principle of assessing risk for decision making on the appropriate use of treatments is well demonstrated in the case-finding strategy of the National Osteoporosis Foundation.¹⁰ Several analytical approaches were devised, based on parameters such as the probability of fracture as a function of age, risk factors and BMD, consequences of fractures and costs, effect on quality of life and trade-offs between benefits, risks and costs. Decisions were to be tailored to individual women based on the values they placed on different outcomes and the cost they were willing to pay to derive benefits.

Another approach has been to derive the absolute risk of fracture (lifetime risk) from age-related relative risks, first fracture incidence and mortality estimates, which may obviate the need for a diagnostic threshold.³¹ The decision for treatment would be based on whether an individual crosses an unacceptable risk level. A further refinement might be to determine risk estimates of established risk factors and to adjust for interrelated factors so that they may be utilised as independent and additive risk functions.

Recently, a self-assessment tool for predicting fracture risk in healthy, postmenopausal Caucasian women has been described,³⁹ which may be helpful in guiding further evaluation and treatment decisions in these women. This tool, which used easily assessed risk factors such as age, prior fracture, maternal fracture, weight, smoking, ability to stand from sitting and BMD, strongly predicted the risk of hip fracture over 5 years.

While awaiting the development of quantitative risk assessment models appropriate to Asian populations, it may be useful at present to base decisions for treatment qualitatively on the presence of prior fractures, older age, lower BMD, and the presence of other risk factors for fracture, falls or bone loss which are independent of BMD. More research is required, however, to determine if treatment based on high fracture risk with or without BMD, actually reduces the occurrence of fractures.

Conclusion

Bone density measurement, although fraught with limitations, remains the method of detecting osteoporosis before fractures occur. Risk factor assessment may facilitate selection of individuals more likely to have osteoporosis and reduce indiscriminate use of relatively

expensive measurement techniques. Although bone density thresholds are widely used as an indication for osteoporosis therapy, developments in risk factor assessment may improve on fracture risk prediction and provide a refinement for deciding on the use of relatively expensive therapeutic options.

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