Guidelines for the early detection of osteoporosis and prediction of fracture risk

Council of the National Osteoporosis Foundation

Objective. To assess methods available in clinical practice for the early detection of osteoporosis and prediction of fracture risk, and to set guidelines for their use. To make recommendations regarding cost-effective screening of asymptomatic subjects by physicians.

Options. Three methods to predict fracture risk are considered: (*i*) clinical risk factor analysis; (*ii*) biochemical tests; and (*iii*) techniques to measure bone mass. Mass (unselected) screening is compared with screening only those at risk of sustaining a fracture. The optimal age/time of screening and therapeutic intervention thresholds are also considered.

Outcomes. The main potential outcomes considered are the morbidity and mortality of advanced osteoporosis and fracture; the accuracy, precision, safety and costs of screening tests; and treatment for those at risk.

Evidence. Based on the results of published recommendations of international osteoporosis societies, World Health Organisation guidelines and expert opinion.

Values. The guidelines were developed by the National Osteoporosis Foundation in conjunction with other specialists and societies. A workshop attended by all the osteodensitometrists in the country was held in August 1994 to obtain consensus on recommendations. There were no major disputes about the content. The guidelines are intended to optimise health care of society as a whole and are not geared to individual patients.

Benefits, harms and costs. Up to 20% of victims of hip fracture die within 1 year and less than 50% ever regain the functional capability to lead an independent life. The cost of acute fracture care in the USA exceeded $10 billion in 1990. Early intervention has been shown to reduce the rate of vertebral and hip fractures by 50 - 70%. The cost of fracture care and of selected screening has not been measured in this country. Measurement of bone mass is safe, accurate and precise.

Recommendations. (*i*) Measurement of bone mass employing dual-energy X-ray absorptiometry (DEXA) is at present the method of choice to predict hip and vertebral fracture risk. A single measurement can correctly identify the majority of those at risk. (*ii*) Densitometric screening of all (asymptomatic) women cannot be recommended, and selective screening according to specific indications is suggested. Densitometry is indicated at any age if the indication is valid. (*iii*) Guidelines for the interpretation of bone mass data, including therapeutic intervention thresholds, are suggested.

Sponsors. The guidelines were developed and funded by the National Osteoporosis Foundation.

Endorsement. Endorsed by the Medical Association of South Africa.

S Afr Med J 1996; **86:** 1113-1116.

Definition and background

Osteoporosis is a systemic disease characterised by a low bone mass and/or qualitative micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk. The disease is common, costly, and associated with a significant morbidity and mortality.[1-9] The treatment of established osteoporosis and skeletal failure is difficult and effective management of this disease involves prevention — hence early detection.

Objective

The objective of this paper is to assess methods available in clinical practice to predict fracture risk and to set guidelines for its use.

Methods

This paper reviews the literature on the three methods that are generally employed to predict fracture risk and sets guidelines for its use. The guideline is an adapted and expanded version of previous recommendations of the Scientific Advisory Board of the American Osteoporosis Foundation,[4] an International Development Conference on Osteoporosis,[2] a recent report of a World Health Organisation Study Group on the assessment of fracture risk,[3] the published literature,[1-13] and local expert opinion.

The guidelines were developed by the National Osteoporosis Foundation (NOF) in conjunction with other interest groups, which included the Society for Endocrinology, Metabolism and Diabetes of Southern Africa, the South African Society of Obstetricians and Gynaecologists and all osteodensitometrists in the country. The draft guidelines were prepared by Stephen Hough, and deliberated by the NOF Council, which includes physicians, gynaecologists, radiologists and orthopaedic surgeons with expertise relevant to the guidelines. A workshop attended by all the osteodensitometrists in the country was held in August 1994 to obtain consensus on recommendations.

Council Members: F. S. Hough (Chairman), C. Schnitzler (Vice-Chairman), B. Ascott-Evans, B. Cassim, D. Davey, W. Mollentze, P. Schneider, E. Sonnendecker

Contact Person: Professor F. S. Hough, National Osteoporosis Foundation, PO Box 481, Bellville, 7535.

There were no major disputes about the content. Patient preferences were not otherwise represented. The project was funded by the NOF.

Assessment of fracture risk

Three methods are generally employed to predict fracture risk:

1. Historic risk factor analysis.
2. Biochemical evaluation.
3. Measurement of bone mineral density.

Historic risk factor analysis

The more important clinical risk factors which may predispose to the development of osteoporosis include:[10]

- a premature menopause (before 45 years of age) and other causes of low sex hormone levels
- alcohol or tobacco abuse
- strong family history of osteoporosis
- drugs toxic to bone (e.g. glucocorticoids)
- malnutrition, a low calcium or energy intake, and eating disorders such as anorexia
- previous history of fracture after minimal trauma
- medical diseases (e.g. endocrine disorders, gastro-intestinal diseases/surgery, malignancies).

The *predictive value* of clinical risk factors to identify high-risk individuals is generally regarded as unsatisfactory. Sensitivity is low (37 - 48%) and more than 50% of patients without any risk factor may still develop osteoporosis.[1-3] Risk factors for different types of osteoporosis (e.g. hip v. spine) and different populations (age, race, gender) may differ greatly, however, and more local epidemiological studies are therefore needed before historical risk factors can be recommended as a suitable screening technique for osteoporosis.

Biochemical parameters

Biochemical tests to assess the *rate of bone turnover* (e.g. serum total and skeletal alkaline phosphatase, osteocalcin, collagen propeptides, and urinary calcium, hydroxyproline, pyridinoline) have been employed to identify individuals at risk.

Osteocalcin (bone Gla-protein), a bone-specific protein produced solely by osteoblasts, is currently regarded as the best marker of bone formation, while urinary deoxypyridinoline (collagen cross-links) is thought to be the most reliable index of bone resorption.[1-3] However, further studies are required before these biochemical parameters can be recommended for routine screening.

Measurement of bone mineral density

Bone mass (bone mineral density: BMD) is the principal determinant of bone strength, accounting for 75 - 85% of the variance of bone strength measured *in vitro*.[1-3] Qualitative, structural properties of bone are said to account for the remaining 15 - 25%, but cannot readily be assessed by currently available techniques.

The exponential increase in fracture incidence with diminishing bone mass has now been firmly established, and *quantitation of bone mass is currently regarded as the best predictor of fractures.*[1-12]

Techniques to measure bone mineral density

Conventional radiology. Conventional radiographs are often employed to assess the severity of established osteoporosis and to monitor the course of the disease. A reduction of vertebral height by 20 - 25% may be regarded as mild osteoporosis, a reduction of 25 - 40% as moderate, and a reduction of more than 40% as severe.[9]

The detection of a low BMD by conventional radiography is notoriously unreliable, however, since 30 - 40% of skeletal mass must be lost before osteopenia can be detected on routine radiographs. Moreover, 20 - 30% of patients with apparent radiographic osteopenia (technical faults) or vertebral fracture (juvenile epiphysitis, old traumatic fracture or even normal variations in vertebral body shape) have a normal BMD and may not be at increased risk of subsequent fractures.[1-5]

Single-energy absorptiometry. Single-photon absorptiometry (SPA) and single-energy X-ray absorptiometry (SXA) are accurate (2 - 5% error) and precise (1 - 2% error), have a low radiation dose (< 1 uSv) and are portable and relatively cheap. Single-energy absorptiometry can only assess appendicular sites, however, and cannot be used to measure the clinically more important axial BMD of the spine or hip.

Dual-energy X-ray absorptiometry. Dual-photon absorptiometry (DPA) and since 1986 dual-energy X-ray absorptiometry (DEXA) are capable of measuring the BMD of the lumbar vertebrae and various hip areas accurately (4 - 8% error), precisely (1 - 3%) and safely (radiation dose of less than 10% of a standard chest radiograph). More recently lateral DEXA and morphometric X-ray absorptiometry (MEXA) have been introduced. Despite theoretical advantages, lateral DEXA, at least with current technology, does not appear to be of clinical advantage, since the precision error is still too high.[11]

Quantitative computed tomography (QCT). QCT can discriminate between the metabolically more active trabecular and cortical bone of the spine which suggests that this technique is more accurate in assessing early bone loss. Compared with DEXA, the precision error (3 - 6%) and radiation dose (50 - 100 uSv) are higher, which makes this technique less ideal for patient follow-up.[12] Currently femoral BMD cannot be assessed employing QCT.

Others. Magnetic resonance imaging (MRI), photon scattering methods and neutron activation analysis are still regarded as experimental techniques. *Ultrasound densitometry* measures both attenuation and velocity of sound and may provide information concerning the structural organisation of bone in addition to BMD. This promising, radiation-free, portable technique has a precision error of only 1 - 3%, but a large population variance and some concerns regarding accuracy *in vivo* necessitate further study.[13]

Choice of technique

To measure bone mass (BMD). The requirements for a single screening test of BMD are the ability to predict fractures, accuracy and precision, a low radiation dose and short scanning time. These requirements are largely met by

DEXA and SXA, and less adequately by QCT. SXA/SPA is accurate, relatively cheap, portable and easy to operate, but can only assess appendicular BMD.

To assess rate of bone loss. The most important requirement of any technique to assess the rate of bone loss is reproducibility. DEXA has the lowest precision error followed by SXA.

Technique of choice. DEXA is currently the technique of choice to predict hip and vertebral fracture risk.

Indications for osteodensitometry

Many potential indications for bone mass measurement have been proposed.[1-7] These range from unselected screening to what must now be regarded as the outdated indications recommended by the Scientific Advisory Board of the American National Osteoporosis Foundation, published in 1989.[4] *The argument for screening all women is poor.*

Clearly, unselected (mass) screening is unlikely to be cost-effective in this country and cannot be supported. The following bona fide indications for bone mass measurement are recommended:

1. Disorders known to affect bone adversely:
- premature menopause, prolonged amenorrhoea
- other causes of hypogonadism
- endocrine diseases, e.g. Cushing's disease, primary hyperparathyroidism, prolactinomas, thyrotoxicosis
- chronic glucocorticoid or anticonvulsant therapy
- chronic immobilisation
- malnutrition, gut disorders or previous surgery, and low-grade malignant disease.

2. As an aid to initiate oestrogen replacement therapy in perimenopausal women at risk of developing osteoporosis.

3. Confirmation of osteopenia suspected from standard radiographs.

4. History of non-traumatic fractures.

5. Presence of a number of historic risk factors (e.g. strong family history, high alcohol intake, past hysterectomy even if ovaries were left intact, history of eating disorders and anorexia).

6. Monitoring of bone mass during treatment for osteoporosis.

When to test

Densitometry is acceptable at any time if the indication is valid.

Bone loss is most marked during the first 5 years after the menopause. Hormone replacement therapy (HRT) is also most valuable in the early postmenopausal years. Densitometry is therefore most often indicated at this time.

Non-HRT therapeutic modalities have recently become available; they are less prone to cause unacceptable side-effects and better tolerated later in life, but are often costly, without the extraskeletal benefits (or the risks) of hormones. Indications for the use of these non-HRT interventions are therefore almost exclusively related to osteoporosis, which strengthens the argument for using bone densitometry to target therapy. There is therefore a good case for screening women in older age groups in addition to perimenopausal women, and an age of 60 years is recommended.[3]

Interpretation of bone mass data

Fracture threshold

Skeletal fracture is primarily determined by absolute bone density, and use of the so-called T score (i.e. expressing the patient's BMD as the deviation from the mean peak BMD of normal young adults) has therefore become the customary method to interpret BMD values. A reduction in the T score of 2 standard deviations (SD) is a commonly used diagnostic criterion for significant osteopenia and coincides with the 'fracture threshold' as determined from differences in BMD of populations with and without fractures.[1-5]

Intervention threshold — diagnostic categories

All intervention thresholds are somewhat arbitrary, and a recent WHO publication suggests that a T score of more than 2.5 SD below the norm identifies that 30% of postmenopausal females with the highest fracture risk.[3]

Based on the T score, four diagnostic categories have been established:

1. $\leq$ 1 SD of the norm = normal
2. 1 - 2.5 SD below the norm = low BMD (osteopenia)
3. > 2.5 SD below the norm, without radiological evidence of fracture = osteoporosis
4. similar to (3), but fractures present = severe osteoporosis.

Patients in (1) are not at risk, whereas intervention in (3) and (4) is nearly always indicated. A decision whether to intervene in those subjects with a T score of 1 - 2.5 SD below normal requires individualisation and could depend upon a subject's age, general health and clinical risk factor analysis. A repeat bone scan 2 - 3 years later and/or biochemical assessment of the rate of bone loss are logical alternatives.

Use of bone mass data to rationalise therapy in established osteoporosis

In patients with established osteoporosis, initial assessment of *severity* and *site(s)* of bone loss may assist in a rational choice of therapy. Moderately severe bone loss argues for pharmacological intervention with antiresorbing agents such as oestrogen, calcium, vitamin D, bisphosphonates or calcitonin. Marked osteopenia may suggest use of bone formation stimulating drugs like enteric-coated fluoride preparations or anabolic steroids. Bone loss is often, but not invariably, generalised. While certain drugs, such as fluoride, are known to improve vertebral bone mass, other drugs may need to be considered if the cortical bone of the hip is predominantly affected.

Finally, *monitoring of BMD* during treatment for osteoporosis should be considered, since individual sensitivity to drugs employed in the management of osteoporosis is well established, with 10 - 30% of patients not responding to conventional doses of, for example, oestrogen or fluoride.[2] This is usually performed every 12 - 24 months, although more frequent follow-up measurements may be indicated in some conditions characterised by a rapid initial bone loss, e.g. steroid-induced osteoporosis.

Summary of recommendations

1. Osteoporosis is a *common* disease, especially in females and in the aged, with a *high morbidity and mortality.*

2. Treatment of established osteoporosis is difficult, but *preventive management* employing hormonal and/or non-hormonal agents is *highly effective* and capable of reducing bone loss and fractures by 50 - 70%.

3. Although trauma, qualitative structural changes and a low bone mass (BMD) all predispose to fractures, the latter is the dominant determinant. Moreover, *only BMD* can currently be measured (and pharmacologically manipulated) as a *predictor of future fractures.*

4. A single determination of *BMD* can correctly identify the majority of those at risk; the *rate of bone loss* can be determined densitometrically and/or biochemically and may complement a single bone mass measurement.

5. *DEXA* is currently the technique of choice to predict hip and vertebral fracture risk.

6. Arguments for the densitometric screening of *all* women are poor and cannot be supported. *Selective screening* according to specific indications (see 'Indications for osteodensitometry') is suggested.

7. Densitometry is most commonly performed in the peri-/early postmenopausal female. The increasing use of expensive, bone-specific non-HRT drugs has emphasised the importance of densitometric screening to target treatment with these drugs. Densitometry is therefore acceptable *at any age if the indication is valid.*

8. Guidelines for the *interpretation* of bone mass data (based on the T score) including *intervention thresholds* are suggested (see 'Interpretation of bone mass data').

REFERENCES

1. Favus MJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism.* 2nd ed. New York: Raven Press, 1993: 223-304.
2. Consensus Development Conference. Prophylaxis and treatment of osteoporosis. *Osteoporos Int* 1991; **1:** 114-117.
3. World Health Organisation. *Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis* (Report of a WHO Study Group). Geneva: WHO, 1994: 1-129.
4. Johnston CC jun, Melton LJ III, Lindsay R, *et al.* Clinical indications for bone mass measurement. *J Bone Miner Res* 1989; **4:** 1-28.
5. Hui SL, Slemenda CW, Johnston CC jun. Age and bone mass as predictors of fracture in a prospective study. *J Clin Invest* 1988; **81:** 1804-1809.
6. Ross PD, Davis JW, Vogel JM, *et al.* A critical review of bone mass and the risk of fractures in osteoporosis. *Calcif Tissue Int* 1990; **46:** 149-161.
7. Jergas M, Genant HK. Current methods and recent advances in the diagnosis of osteoporosis. *Arthritis Rheum* 1993; **36:** 1649-1662.
8. Black D, Cummins SR, Genant HK, *et al.* Axial and appendicular bone density predict fractures in older women. *J Bone Miner Res* 1992; **7:** 633-638.
9. Genant HK, Wu CY, van Kuijk C, *et al.* Vertebral fracture assessment using a semi-quantitative technique. *J Bone Miner Res* 1993; **8:** 1137-1148.
10. Blaauw R, Albertse E, Beneke T, *et al.* Risk factors for the development of osteoporosis in a South African population. *S Afr Med J* 1994; **84:** 328-332.
11. Delmas PD, ed. Osteoporosis: who should be treated? (Proceedings of a Symposium). *Am J Med* 1995; **98**(2A): 2A-1S — 2A-88S.
12. Pacifici R, Rudolph R, Griffin M, *et al.* Dual energy radiography versus quantitative computer tomography for the diagnosis of osteoporosis. *J Clin Endocrinol Metab* 1990; **70:** 705-710.
13. Heany RP, Avioli LV, Chestnut CH, *et al.* Osteoporotic bone fragility: detection by ultrasound transmission velocity. *JAMA* 1989; **2:** 2986-2990.