Osteoporosis III

Diagnosis of osteoporosis and assessment of fracture risk

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The diagnosis of osteoporosis centres on the assessment of bone mineral density (BMD). Osteoporosis is defined as a BMD 2·5 SD or more below the average value for premenopausal women (T score <–2·5 SD). Severe osteoporosis denotes osteoporosis in the presence of one or more fragility fractures. The same absolute value for BMD used in women can be used in men. The recommended site for diagnosis is the proximal femur with dual energy X-ray absorptiometry (DXA). Other sites and validated techniques, however, can be used for fracture prediction. Although hip fracture prediction with BMD alone is at least as good as blood pressure readings to predict stroke, the predictive value of BMD can be enhanced by use of other factors, such as biochemical indices of bone resorption and clinical risk factors. Clinical risk factors that contribute to fracture risk independently of BMD include age, previous fragility fracture, premature menopause, a family history of hip fracture, and the use of oral corticosteroids. In the absence of validated population screening strategies, a case finding strategy is recommended based on the finding of risk factors. Treatment should be considered in individuals subsequently shown to have a high fracture risk. Because of the many techniques available for fracture risk assessment, the 10-year probability of fracture is the desirable measurement to determine intervention thresholds. Many treatments can be provided cost-effectively to men and women if hip fracture probability over 10 years ranges from 2% to 10% dependent on age.

Introduction

As prevalence and awareness of osteoporosis increases, and treatments of proven efficacy become available, the demand for management of patients with the disease will also rise. Such demand will, in turn, require widespread development of facilities for the diagnosis and assessment of osteoporosis. Measurement of bone mineral density (BMD) is the central component of any provision that arises from the internationally agreed definition of osteoporosis: a 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.[1] The diagnosis of osteoporosis thus centres on assessment of bone mass and quality. There are no satisfactory clinical means to assess bone quality. Diagnosis of osteoporosis, therefore, depends on the measurement of skeletal mass.

The clinical significance of osteoporosis rests with the fractures that arise as a consequence of the condition, and their attendant morbidity and mortality. Low bone mass is an important component of the risk of fracture, but other abnormalities arise in the skeleton that contribute to skeletal fragility. Furthermore, various non-skeletal factors, such as the liability to fall, contribute to fracture risk. Thus, ideally, assessment of fracture risk should encompass all these aspects. There is, therefore, a distinction to be made between diagnosis of osteoporosis and assessment of risk, which in turn implies a distinction between diagnostic and intervention thresholds.

Search strategy

This article is based on review of international publications collected by the author during his time working in the specialty.

Lancet 2002; **359:** 1929–36

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Measurement of bone mineral content

Single and dual X-ray absorptiometry

Single and dual X-ray absorptiometry (DXA) are used to assess mineral content of the entire skeleton and that of specific sites, including those most vulnerable to fracture.[2] Bone mineral content is the amount of mineral in the specific site scanned and, when divided by the area measured, can be used to derive a value for BMD. Both techniques provide a two-dimensional, areal picture, rather than a true volumetric density. Thus, the size of the bone affects the apparent density, since the relation between area and volume is non-linear. Paradoxically, this error can improve the value of BMD as a predictor of fracture risk, since bone size is also a determinant of skeletal strength.

Panel 1: **Sources of error in the diagnosis of osteoporosis by dual X-ray absortiometry[4]**

Incorrect diagnosis of osteoporosis caused by:
Osteomalacia
Osteoarthritis (of spine but also of the hip)
Soft tissue calcification (especially aortic calcification for spine measurements)
Overlying metal objects
Contrast media
Previous fracture (spine, hip, and wrist)
Severe scoliosis
Extreme obesity or ascites
Vertebral deformities due to osteoarthritis, Scheuermann's disease
Inadequate reference ranges
Inadequate operating procedures—eg, calibration, region selection, acquisition mode, positioning)

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The accuracy of DXA at the hip exceeds 90%;[3] residual errors arise for various reasons, related to the technique itself and the manner in which it is applied. Panel 1 shows some of the causes of diagnostic errors of clinical importance.[4]

BMD is an index of bone mass only when bone is fully mineralised. The presence of osteomalacia, often a complication caused by poor nutrition in elderly people, will, therefore, result in underestimation of bone mass. Osteoarthritis at the spine or the hip is common in the elderly, and contributes to the density measurement but not necessarily to skeletal strength. Heterogeneity of density because of osteoarthritis or previous fracture can often be detected on the scan, and in some instances can be excluded from the analysis. In the case of the hip, other regions of interest such as the femoral neck can be selected to exclude the joint.

Ultrasonic measurement of bone

Skeletal status in osteoporosis can be measured with quantitative ultrasound methods. The most widely assessed methods are broad-band ultrasound attenuation and speed of sound (or ultrasound velocity) at the heel. Because these techniques do not involve ionising radiation and could provide some information with respect to the structural organisation of bone in addition to bone mass, there is much interest in their use. For reasons outlined below, these techniques cannot be used to diagnose osteoporosis, but evidence[5–8] lends support to their use for the assessment of fracture risk in elderly women.

Computed tomography

Quantitative computed tomography has been applied both to the appendicular skeleton and to the spine.[9–11] Conventional whole body computed tomography scanners need calibration to convert their results into units relevant to BMD. Quantitative computed tomography is most useful in the assessment of cancellous bone density because it provides a measure of true volumetric density, rather than an area-adjusted result (as is the case with DXA). Cancellous bone is more responsive than cortical bone to many interventions. Computed tomography can, therefore, be used to monitor the effect of treatment.[2] Additionally, the technique avoids the effect of degenerative disease, a particular drawback to DXA at the spine. The main disadvantages of computed tomography are high exposure to radiation, difficulties with quality control, and high cost compared with DXA.

Radiography

Osteoporosis can often be diagnosed by looking at simple radiographs, albeit with low sensitivity. Furthermore, there are several characteristic features of osteoporosis that can be seen with this technique, which help in diagnosis or in differential diagnosis. Subclinical vertebral fracture is a strong risk factor for subsequent fractures, for example, both at new vertebral sites and at other sites susceptible to osteoporosis. There is, therefore, great interest in the identification of vertebral deformities due to osteoporosis that might not have otherwise come to clinical attention.

Of the many techniques that have been developed to assess bone mass, bone mineral content, or other related aspects of skeletal mass or structure, the technique that has been paid the greatest amount of attention in terms of technical development and biological validation is DXA, which is regarded as the gold standard for diagnosis.[12] The adoption of DXA as a reference standard provides a technique against which the performance characteristics of less well established methods can be compared for the several applications of densitometry—eg, diagnosis of osteoporosis, assessment of prognosis (fracture prediction), monitoring of the natural history of the disorder, and assessment of response to treatment.

Diagnosis of osteoporosis

The easiest way to diagnose osteoporosis by bone density measurements is to define a threshold—namely, a cutoff for BMD, that encompasses most patients with osteoporotic fractures. Bone density measurements are, however, also used to assess future risk of fracture, so that more than one cutoff is needed.

Thresholds

Skeletal mass and density remain fairly constant, once growth has stopped, until about age 50 years.[13] The distribution or density of bone mineral content in young healthy adults (peak bone mass) is appoximately Gaussian normal irrespective of the technique used. Because of the Gaussian distribution, bone density values in individuals can be expressed in relation to a reference population in standard deviation (SD) units. This ability reduces the difficulties associated with differences in calibration between instruments. When SDs are used in relation to the young healthy population, this measurement is referred to as the T score.

For women, four general diagnostic categories have been proposed by WHO and modified by the International Osteoporosis Foundation, for assessments done with DXA:[3,12]

- Normal—hip BMD greater than 1 SD below the young adult female reference mean (T score ⩾–1).
- Low bone mass (osteopenia)—hip BMD greater than 1 SD below the young adult female mean, but less than 2·5 SD below this value (T score <–1 and >–2·5).
- Osteoporosis—hip BMD 2·5 SD or more below the young adult female mean (T score ⩽–2·5).
- Severe osteoporosis (established osteoporosis)—hip BMD 2·5 SD or more below the young adult mean in the presence of one or more fragility fractures.

In women, bone loss occurs predominantly after the menopause. In the young healthy population, 15% of women have a T score of less than –1 and thus have low bone mass or osteopenia (figure 1).[14,15] Because of the normal distribution for BMD, about 0·5% of women fall into the osteoporotic range, with a T score of –2·5 or less.[14] Furthermore, the proportion of women affected by

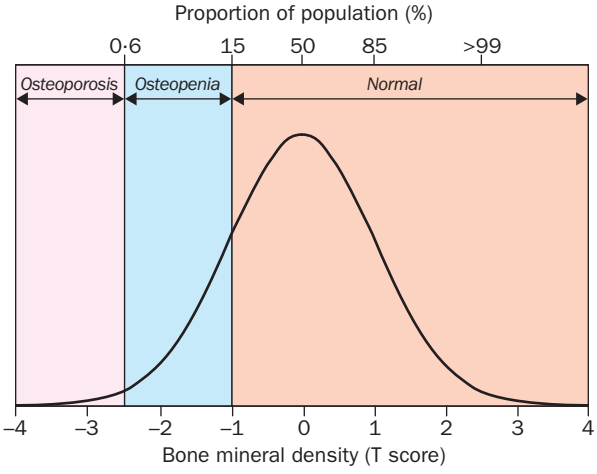

Figure 1: **Distribution of bone mineral density in healthy women aged 30–40 years**

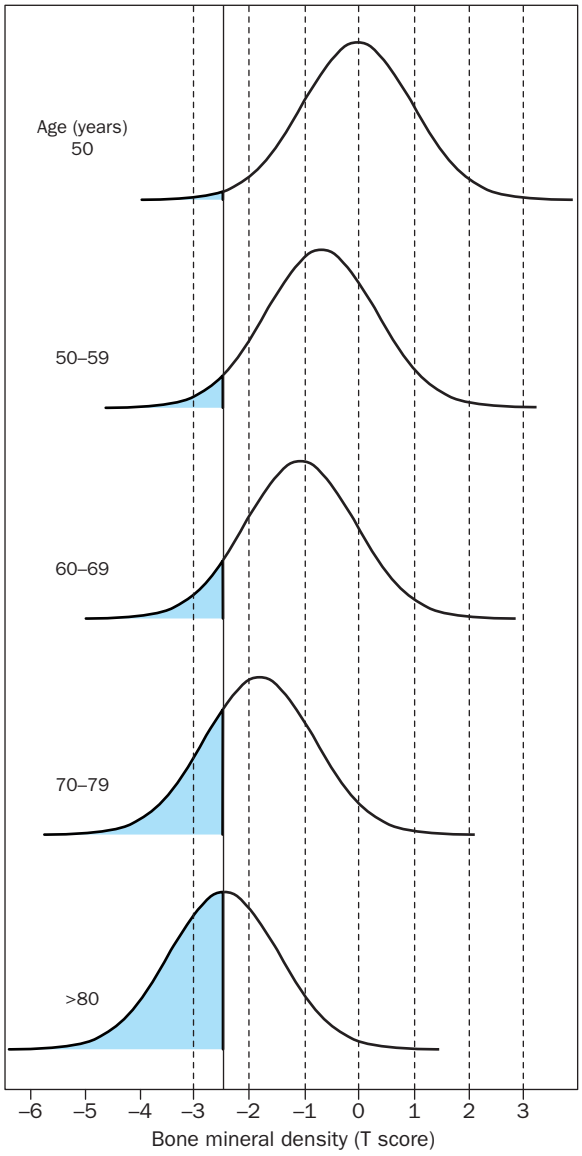

Figure 2: **Distribution of bone mineral density in women of different ages, and the prevalence of osteoporosis (blue)[14]**
T score below –2·5=osteoporosis. Reproduced from reference 14 by permission of the American Society for Bone and Mineral Research.

osteoporosis at any one anatomical site increases greatly with age in much the same way as fracture risk increases with age (figure 2).[14] Indeed, the increase in prevalence is roughly exponential and conforms to the known pattern of frequency of many osteoporotic fractures in ageing women. When measurements are made at one site, for example at the hip, then the prevalence of osteoporosis of the hip in white women aged 50 years or more is about one in six, which is close to the life-time risk of hip fracture.[16]

Sites and techniques

The T score cannot be used, for diagnosis, interchangeably with different techniques or be based on measurements taken from different sites, since the same T score derived from different sites and with different techniques yields different information on fracture risk. Reasons for this variation include differences in the gradient of risk for techniques to predict fracture, discrepancies in the population SDs, and differences in the apparent rates of bone loss with age.[12,17] A further difficulty is that the intersite correlations, though usually significant, are inadequate for prediction, giving rise to errors of misclassification[18,19] because of biological variations in BMD, and because of technical errors of accuracy. The same holds true in principle for many other multifactorial diseases. For example, in hypertension, measurements made at the leg can differ substantially from measurements made at the arm. In the specialty of hypertension, to select a standardised site for diagnosis is appropriate, though such standardisation should not negate the use of other sites (or techniques) for risk assessment.

For diagnosis, measurement at the hip is the gold standard in terms of site, since it has the highest predictive value for hip fracture,[20] which is the most severe complication of osteoporosis and predicts risk of all fractures as well as other techniques. These considerations should not be taken to infer that other techniques and measurements with DXA at other sites are not useful. Indeed they are for risk assessment rather than for diagnosis.

Diagnosis in men

Suitable diagnostic cutoff values for men are less well defined than for women. Many studies[21–25] have examined fracture risk in men and women and have variously concluded that the risk rises with decreasing BMD, or the fracture threshold is the same or differs between sexes. There are several reasons for these discrepancies. First, the relation between BMD and fracture risk changes with age,[26,27] so that age adjustment is required. Second, a difference between sexes in the gradient of risk (relative risk per SD increase in BMD) could be a result of differences in the SD of measurements. Third, data from referral populations of osteoporotic men and women could be biased. These difficulties are overcome by sampling populations at random and expressing risk as a function of BMD or standardised T scores, with age adjustment. The few studies available[28,29] show that the risk of hip fracture is similar in men and women for any given BMD. Such studies indicate that a similar cutoff value for hip BMD that is used in women can be used in the diagnosis of osteoporosis in men—namely, a value for BMD 2·5 SDs or more below the average for women.[12]

Reference ranges

Of particular importance is the type of normal reference range used, which should be taken from appropriate populations. Small differences between ranges have a large effect on the number of individuals with BMD below a diagnostic threshold. The current recommendation of the International Osteoporosis Foundation and WHO is to use the National Health and Nutrition Examination Survey (NHANES) reference database in women aged 20–29 years as the reference range.[12]

Assessment of fracture risk

DXA and quantitative ultrasound

The clinical consequence of osteoporosis is the fractures that arise. There is, therefore, a great deal of interest in the prognostic use of bone mineral measurements—namely, their ability to predict the likelihood of fractures. In this sense the accuracy of the techniques is not how closely they measure BMD, but their sensitivity and specificity to predict fractures. Many well controlled prospective studies with DXA, particularly in elderly women, indicate that the risk of fracture about doubles for each SD reduction in BMD (table 1).[20]

The gradient of risk (increase in fracture risk for specific change in BMD) depends on the technique used, the site

	Forearm fracture	Hip fracture	Vertebral fracture	All fractures
Site of measurement				
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)

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Table 1: **Age-adjusted relative increase in risk of fracture (with 95% CI) in women for every 1 SD decrease in bone mineral density (absorptiometry) below the mean value for age[20]**

measured, and the fracture of interest. In general, site-specific measurements show the higher gradients of risk for their respective sites. For example, measurements at the hip predict hip fracture with greater power than do measurements at lumbar spine or forearm. Gradients of risk range from 1·5 to 3·0 for each SD decrease in bone mineral measurement (table 1). Gradients of risk for different sites are independent of age. The performance characteristics of ultrasound are similar for prognostic use. Results of most studies suggest that measurements of broad band ultrasound attenuation or speed of sound are associated with a 1·5-fold to 2·0-fold increase in risk for each SD reduction in BMD.[5] Findings of some, but not all, studies suggest that ultrasound might measure some aspects of skeletal status and fragility that cannot be measured with absorptiometric techniques alone.[7,30,31]

Panel 2: **Risk factors for osteoporotic fractures**

Female sex
Premature menopause
Age*
Primary or secondary amenorrhoea
Primary and secondary hypogonadism in man
Asian or white ethnic origin
Previous fragility fracture*
Low bone mineral density
Glucocorticoid therapy*
High bone turnover*
Family history of hip fracture*
Poor visual acuity*
Low bodyweight*
Neuromuscular disorders*
Cigarette smoking*
Excessive alcohol consumption
Long-term immobilisation
Low dietary calcium intake
Vitamin D deficiency

*Characteristics that capture aspects of fracture risk over and above that provided by bone mineral density.

Estimation of fracture risk by BMD measurements is similar to the assessment of the risk of stroke by blood pressure readings. Blood pressure values are continuously distributed in the population, as is BMD. In the same way that a patient above a cutoff for blood pressure is diagnosed as hypertensive, the diagnosis of osteoporosis is based on a value for BMD below a cutoff threshold. As is the case for blood pressure, there is no threshold of BMD that discriminates absolutely between those who will or will not have a clinical event. The ability to predict hip fracture by measurement of BMD is, however, at least as good as that of blood pressure in predicting stroke, and considerably better than the use of serum cholesterol to predict coronary artery disease.[3,32] Nevertheless, that a normal BMD measurement is no guarantee that fracture will not occur should be recognised—only that the risk is reduced. Conversely, if BMD is in the osteoporotic range, then fractures are more likely. At age 50 years, the proportion of women with osteoporosis who will fracture their hip, spine, or forearm or proximal humerus in the next 10 years—ie, positive predictive value—is about 45%. The detection rate for these fractures (sensitivity) is, however, low, and 96% of such fractures would arise in women without osteoporosis.[33] Low sensitivity is one of the reasons why widespread population-based screening is not recommended in women at the menopause.[3]

Biochemical assessment of fracture risk

Biochemical indices of bone turnover can be divided into two groups: markers of resorption and markers of formation.[34] The principal markers of bone formation are total alkaline phosphatase, the bone isoenzyme alkaline phosphatase, osteocalcin, and the procollagen propeptides of type I collagen. The most widely used markers of bone resorption are hydroxyproline, and the pyridinium crosslinks and their associated peptides.

Bone markers are increased after the menopause, and the results of several studies indicate that the rate of bone loss varies according to the marker value. Thus a potential clinical application of biochemical indices of skeletal metabolism is in assessment of fracture risk. Findings of prospective studies indicate an association between osteoporotic fracture and indices of bone turnover, independent of bone density in women at the menopause[35,36] and in elderly women.[37] In elderly women with values for resorption markers that exceed the reference range for premenopausal women, fracture risk is increased about two-fold after adjustment for BMD. These results suggest that a combined approach, with BMD and indices of bone turnover, could improve fracture prediction in postmenopausal women.[38]

Clinical risk factors

Many risk factors for osteoporosis have been identified (panel 2). In general, risk factor scores show poor specificity and sensitivity in prediction of either BMD or fracture risk.[39–42] Moreover, some risk factors vary in importance according to age. For example, risk factors for falling—eg, visual impairment, reduced mobility, and treatment with sedatives—are more strongly predictive of fracture in the elderly than in younger individuals.[43]

Hypogonadism is an important risk factor for osteoporosis in both sexes. In young women, hypogonadism can be primary or secondary to conditions such as anorexia nervosa, exercise-induced amenorrhoea, chronic illness, hyperprolactinaemia, and gynaecological disorders. Premature menopause, either spontaneous or induced by surgery, chemotherapy, or radiotherapy is also associated with increased risk of osteoporosis. In men, hypogonadism can be caused by various disorders, including Klinefelter's syndrome, hypopituitarism, hyperprolactinaemia, and castration—for example, after prostatic surgery.

Glucocorticoids are an important cause of osteoporosis. Bone loss is believed to be most rapid in the first few months of treatment and affects both the axial and appendicular skeleton, but is most pronounced at the spine, where cancellous bone predominates. Bone loss can be avoided by inhaled glucocorticoid therapy.[44] Although the skeletal response to glucocorticoids varies between individuals, high doses are generally associated with greater adverse skeletal effects, whereas daily doses of

prednisolone below 7·5 mg are less likely to result in increased rates of bone loss and fracture.[45]

Furthermore, a history of fragility fracture is an important risk factor for further fracture—eg, risk of subsequent fracture of the hip is increased by more than two-fold after previous fracture of the hip or spine. This risk is reduced though still present if the site of previous fracture is the forearm (risk increased by 1·9) or the proximal humerus (2·0). Risk of fracture of the spine is similarly increased after a previous break at the hip (2·5), the spine (4·4), the forearm (1·7), or the proximal humerus (1·9).[46] The presence of two or more prevalent vertebral fractures is associated with a 12-fold increase in fracture risk for any specific BMD.[47]

Results of case-control studies of hip fractures in men and women show an increased risk of fracture with disorders associated with secondary osteoporosis, such as previous hyperthyroidism, gastric surgery, and hypogonadism.[39,48–50] There is also a greater risk of hip fracture with conditions related to an increased risk of falling, such as hemiparesis, Parkinson's disease, dementia, vertigo, alcoholism, and blindness.[24,48]

Of the risk factors shown in panel 2, smoking, alcohol, and poor calcium nutrition are weak risks. Complete immobilisation leads to rapid bone loss at the affected sites, but evidence that lesser degrees of physical inactivity increase the risk of osteoporosis is not so well documented. A low body-mass index is an important risk factor for osteoporosis and fractures, probably because of its association with bone size. Finally, a parental history of hip fracture is an independent risk factor for fracture. For any specific BMD, hip fracture risk is increased about two-fold.[40]

Identification of individuals for treatment

At present there is no universally accepted policy for screening to identify individuals at high risk of fracture. The test used to diagnose osteoporosis, bone densitometry, has low sensitivity (detection rate) at acceptable specificity. Thus, the risk of fracture is very high when osteoporosis is present, but the risk of fracture is by no means negligible when BMD is normal (figure 3). Because factors in addition to BMD can be measured that contribute independently to fracture risk, screening strategies for fracture prediction might be developed in the future. Such a strategy is likely to be targeted to elderly people, in whom fracture probability is higher, as too is the prevalence of many of the risk factors, than in women at the menopause. In the absence of a validated screening strategy, a case finding strategy is recommended in which patients are identified because of a fragility fracture or by the presence of other strong risk factors for fracture, and thereafter assessed by BMD measurement (panel 3). This strategy forms the basis of a case-finding approach widely used in Europe and the USA.[4,51,52]

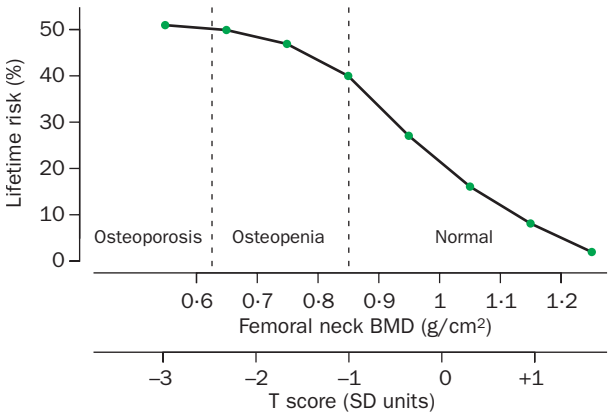

Figure 3: **Remaining lifetime risk of hip fracture in women aged 50 years, according to bone mineral density (BMD) or T score at the hip**

Panel 3: **Risk factors that provide indications for the diagnostic use of bone densitometry[4]**

- **Presence of strong risk factors**

Oestrogen status
Premature menopause (<45 years)
Long-term secondary amenorrhoea (>1 year)
Primary hypogonadism

Corticosteroid therapy
Prednisolone (or equivalent) 7·5 mg per day or more with an expected use of more than 6 months

Maternal family history of hip fracture

Low body-mass index (<19 kg/m²)

Other disorders associated with osteoporosis
Anorexia nervosa
Malabsorption syndromes, including chronic liver disease and inflammatory bowel disease
Primary hyperparathyroidism
Post-transplantation
Chronic renal failure
Hyperthyroidism
Long-term immobilisation
Cushing's syndrome

- **Radiographic evidence of osteopenia or vertebral deformity or both**
- **Previous fragility fracture, especially of the spine or wrist**
- **Loss of height, thoracic kyphosis (after radiographic confirmation of vertebral deformities)**

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In Europe, treatment is recommended in the presence of osteoporosis, but in the USA less stringent criteria are used. Not all patients with such risk factors need diagnostic assessment. For example, patients with more than one vertebral fracture should be offered treatment irrespective of their bone density, although the measurement could help to monitor treatment effect.

The use of risk factors that add information on fracture risk independently of BMD (see panel 2) improves the sensitivity of the assessment for any specificity.[33,53] Such factors can be used to enhance the case-finding strategy, although some care is needed in the use of density independent risk factors to identify individuals for drug treatments that affect skeletal metabolism. For example, inhibitors of bone turnover might not be effective in populations selected on the basis of a fall. With this proviso, independent risk factors could be used to enhance the predictive value of BMD.

An example of the use of independent risk factors is provided by the interaction of biochemical markers of skeletal turnover and BMD. Results of the EPIDOS study[54] show independent contributions of BMD and urinary resorption markers on hip fracture risk in elderly women with a mean age of 81 years.[54] At this age, the average remaining 10-year risk of hip fracture is 15%. By selecting women with osteoporosis, the 10-year risk for

	Age (years)			
	50	60	70	80
Relative risk				
Hip fracture				
Men				
1	0·84	1·26	3·68	9·53
2	1·68	2·50	7·21	17·89
3	2·51	3·73	10·59	25·26
4	3·33	4·94	13·83	31·75
Women				
1	0·57	2·40	7·87	18·0
2	1·14	4·75	15·1	32·0
3	1·71	7·04	21·7	42·9
4	2·27	9·27	27·7	51·6
Hip, clinical spine, humeral, or Colles' fracture				
Men				
1	3·3	4·7	7·0	12·6
2	6·5	9·1	13·5	23·1
3	9·6	13·3	19·4	13·9
4	12·6	17·3	24·9	39·3
Women				
1	5·8	9·6	16·1	21·5
2	11·3	18·2	29·4	37·4
3	16·5	26·0	40·0	49·2
4	21·4	33·1	49·5	58·1

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Table 2: **10-year probability of fracture (%) in men and women from Sweden, according to age and risk relative to the average population[33]**

hip fractures rises to 25%. Selection of women on the basis of values for urinary markers above the premenopausal range shows a risk of 33%. With the combination of low hip BMD and high resorption markers, the 10-year fracture risk is 49%.[38] Such considerations have led to the view that intervention thresholds should be based on fracture risk rather than on any particular level of BMD.

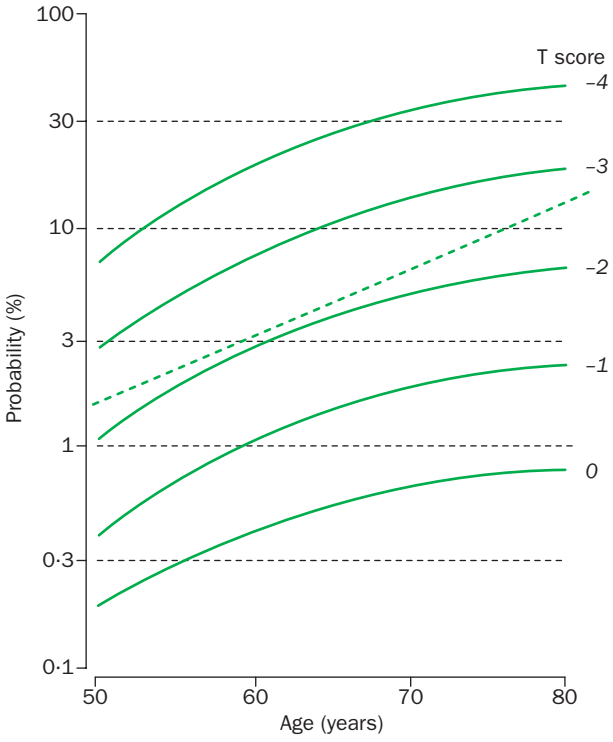

Figure 4: **10-year probability of hip fracture in Swedish men and women, according to T scores assessed at the femoral neck by dual X-ray absorptiometry**

Probability scale is logarithmic. Green dotted line=probability at which interventions are cost effective.[26,59] Reproduced from reference 26 by permission of Osteoporosis International.

The use of high gradients of fracture risk by combining risk factors not only improves the detection rate, but also enlarges the population that can be selected with a particular threshold of risk. Say, for example, one wanted to identify individuals with a risk of fracture three times greater than the average risk for the general population, a test with a gradient of risk of 2·0 SD would identify 2·7% of the population, but a test with a gradient of risk of 3·0 SD would detect 6·1% of the population.[55]

Intervention thresholds

Absolute risk depends on age and life expectancy as well as present relative risk.[56] Estimates of lifetime risks are of value in considering the burden of osteoporosis in the community and the effects of intervention strategies. For several reasons they are less relevant for assessment of risk of individuals in whom treatment might be envisaged. First, treatments are not prescribed for a lifetime, because of side-effects of continued treatment—eg, hormone replacement therapy—or low compliance. Moreover, the feasibility of lifelong interventions has not been tested with either high risk or global strategies.[52] Second, the predictive value of low BMD and some other risk factors for fracture risk is attenuated over time.[57] Finally, the confidence in estimates falls with time because of uncertainties about future mortality trends. For this reason, the International Osteoporosis Foundation and WHO recommend that risk of fracture should be expressed as an absolute risk—ie, probability—over 10 years.[12] This period covers the probable duration of treatment and benefits that might continue once treatment is stopped.[58]

Table 2 shows the 10-year fracture probabilities for the common osteoporotic fractures, according to the population relative risk.[33] Note that the probabilities are derived from Swedish data, which show a high incidence of fracture and should be adjusted downwards for countries where the age-specific risk is low. Probabilities can similarly be derived from the T-score result of BMD assessment (figure 4).[26,59]

Since the aim of the assessment of fracture risk is to target interventions accurately to those at highest risk, and avoid treatment of those at low risk, an important question is what is the cut off value for relative risk, BMD, or 10-year risk that provides an intervention threshold. This issue is complex and depends on clinical practice, effectiveness of treatment (compliance, continuance, and efficacy), side-effects of treatment, the type of fracture expected, and the costs of treatment. Several agencies in Europe and the USA have constructed evidence-based practice guidelines in which intervention thresholds are based on health economic analyses.[4,51,52] Although there are important differences between the approaches,[60] these agencies would agree that for most interventions envisaged, individuals with osteoporosis should be offered treatment, which can be justified from a health economics perspective.

When hip fracture alone is considered, a 10-year probability of 10% or more provides a cost-effective threshold for women in Sweden.[61] However, many fractures other than hip fracture also contribute to morbidity, particularly in the young in whom hip fractures are rare. When account is taken of such fractures,[62] cost-effective intervention probabilities decrease, especially in young individuals (figure 4).[59] Note that cost-effective interventions can be provided to most women with osteoporosis.

Conclusions

The diagnosis of osteoporosis is generally based on assessment of BMD at the proximal femur by DXA. By contrast, intervention thresholds should be based on fracture probability. Several clinical risk factors for fracture with and without BMD allow the more accurate stratification of risk than the use of BMD alone. In the absence of validated screening strategies, a case-finding approach is advocated for individuals with strong risk factors who are referred for BMD assessment. Intervention is best targeted to those in whom fracture probability exceeds a threshold of reversible risk, based on cost-effectiveness.

Conflict of interest statement

J A Kanis has received research funding and done ad-hoc consultancies for most companies with an interest in osteoporosis, and has equity in British Biotec, UK; Celtrix, USA; Glaxo, UK; Lilly, USA; Merck, USA; Novo Nordisk, Denmark; Procter and Gamble, USA; Shire, UK; Strakan, UK; and Unigene, USA.

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Uses of error

The dangers of conformity

John Swales

Let me start by stating categorically that there is no shortage of clinical errors in my professional career. A spell as a pre-registration casualty officer in a London hospital allowed me to contribute a sizeable quota to the misdiagnosed chest pains and overlooked fractured scaphoids that finally led to the merciful abolition of such junior posts. I learnt one thing from these experiences: the fundamental mistake is failure to recognise when someone is genuinely ill or in pain. Without the ability to do this, textbook knowledge is singularly futile. My memorable error is somewhat different, although I hope that the lesson is also broadly applicable. In the early 1970's malignant hypertension was much more common than it is today. Hypertension clinics cared for substantial numbers of such patients who unquestionably owed their lives to complicated and often fairly unpleasant medication. Their survival was in some ways a source of pride at a time when treating milder forms of hypertension was still being questioned.

One of the patients who had been rescued by anti-hypertensive treatment had presented a couple of years before to the emergency room with malignant hypertension. He differed from the other patients as he was a chronic schizophrenic and would express rather pathetic gratitude for our interest, but otherwise said little. By the time I came to know him he owed, I felt, less to us than to his sister, who lived with him, looked after him and invariably accompanied him to hospital. He was clearly totally dependent on her. On this occasion the ritual of clinical enquiry and his blood pressure measurement was over when she murmured in a curiously forced, yet off-hand way that she had been suffering from headaches. I had no difficulty in recognising the hidden importance of what was being said by my patient's sister. My response was professionally correct—to suggest as sympathetically as I could that she should make an appointment to see her doctor as soon as possible. I do not know whether she did or not. At his next visit, my patient came alone. His sister had died of a cerebral haemorrhage and uncontrolled hypertension shortly after seeing me.

What I did was consistent with professional etiquette. She did not obviously need emergency treatment on the day I saw her and she was already under her GP's care. To employ that language of possession that we owe to the nineteenth century, she was not my patient. Of course, I could have done more, even within the limits of professional guidance. I could have spoken to her GP and offered help, and he may well have welcomed some advice. But that is not my major concern. My regret is that I allowed a rigid view of professional etiquette to dictate what I did against my initial instinct and this ruined two lives. It would have been quite straightforward to take her blood pressure and look at her fundi. Medicine at times demands that the wrong thing is done for the right reasons. I should have done the wrong thing. That was my error.

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Prof J Swales died on October 17, 2000