Osteoporos Int (2005) 16: 581–589
DOI 10.1007/s00198-004-1780-5

REVIEW

Assessment of fracture risk

**John A. Kanis · Frederik Borgstrom · Chris De Laet
Helena Johansson · Olof Johnell · Bengt Jonsson
Anders Oden · Niklas Zethraeus · Bruce Pfleger
Nikolai Khaltaev**

Received: 13 September 2004 / Accepted: 15 September 2004 / Published online: 23 December 2004

Abstract The diagnosis of osteoporosis is based on the measurement of bone mineral density (BMD). There are a number of clinical risk factors that provide information on fracture risk over and above that given by BMD. The assessment of fracture risk thus needs to be distinguished from diagnosis to take account of the independent value of the clinical risk factors. These include age, a prior fragility fracture, a parental history of hip fracture, smoking, use of systemic corticosteroids, excess alcohol intake and rheumatoid arthritis. The independent contribution of these risk factors can be integrated by the calculation of fracture probability with or without the use of BMD. Treatment can then be offered to those identified to have a fracture probability greater than an intervention threshold.

J.A. Kanis (✉)
Centre for Metabolic Bone Diseases
(WHO Collaborating Centre),
University of Sheffield Medical School,
Beech Hill Road, Sheffield, S10 2RX, UK
E-mail: w.j.pontefract@sheffield.ac.uk
Tel.: +44-114-2851109
Fax: +44-114-2851813

F. Borgstrom
Stockholm Health Economics, Stockholm, Sweden

C. De Laet
Scientific Institute of Public Health, Brussels, Belgium

H. Johansson · A. Oden
Solberg 8414, S-442 92, Romelanda, Sweden

O. Johnell
Department of Orthopaedics, Malmo General Hospital,
Malmo, Sweden

N. Zethraeus
Centre for Health, Stockholm School of Economics,
Stockholm, Sweden

B. Pfleger
Atlanta, Ga., USA

N. Khaltaev
Geneva, Switzerland

Keywords Case-finding · Clinical risk factors · Fracture probability · Intervention threshold

Introduction

The increasing prevalence and awareness of osteoporosis, together with the development of treatments of proven efficacy, will increase the demand for management of patients with osteoporosis. This in turn will require widespread facilities for the assessment of osteoporosis. Measurements of bone mineral are a central component of any provision that arises from the internationally agreed description of osteoporosis: a systemic 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 thus centres on the assessment of bone mass and quality. There are no satisfactory clinical tools available to assess bone quality independently of bone density, so that for practical purposes the diagnosis of osteoporosis depends upon the measurement of skeletal mass, as assessed by measurements of bone mineral density (BMD).

The clinical significance of osteoporosis is the fractures that arise with their attendant morbidity and mortality. Although bone mass is an important component of the risk of fracture, other abnormalities occur in the skeleton that contribute to fragility. In addition, a variety of non-skeletal factors, such as the liability to fall and force of impact, contribute to fracture risk. Since BMD forms but one component of fracture risk, accurate assessment of fracture risk should ideally take into account other readily measured indices of fracture risk that add further information to that provided by BMD.

The identification of risk factors for fracture has been widely used in case finding strategies. In such schemes, patients are identified on the basis of clinical risk factors. Examples include a family history of fragility fracture, a

previous fragility fracture, low body mass index and the long-term use of corticosteroids. Patients so identified are referred for bone mineral density measurements, and intervention offered if bone mineral density falls below a given threshold. Current guidelines in Europe suggest that intervention should be offered in those individuals subsequently shown to have osteoporosis (i.e. a *T*-score of –2.5 SD or less) [2,3]. In the USA, a less stringent threshold is recommended of –2.0 SD in the absence of significant risk factors, and –1.5 SD in the presence of risk factors [4]. This case finding strategy is conservative. Individuals must have one of the chosen risk factors before they are referred for bone mineral density under the current guidance of the International Osteoporosis Foundation (IOF). Moreover, the vast majority of fractures will occur in those individuals who are never assessed. Against this background, a growing view is that the assessment of fracture risk should encompass all aspects of risk and that intervention should not be guided solely on the basis of BMD [5,6]. There is a distinction to be made, therefore, between diagnosis of osteoporosis and the assessment of fracture risk, that in turn implies a distinction between diagnostic and intervention thresholds. This paper reviews the extent that this can be achieved in clinical practice.

Table 1 Prevalence (%) of osteoporosis at the age interval shown in Sweden using female-derived thresholds from the young population aged 20–29 years

Age range (years)	Men (%)	Women (%)
50–54	2.5	6.3
50–59	3.5	9.6
60–64	5.8	14.3
65–69	7.4	20.2
70–74	7.8	27.9
75–79	10.3	37.5
80–84	16.6	47.2
50–84	6.3	21.2

Bone mineral density

The cornerstone for the diagnosis of osteoporosis lies in the assessment of BMD. In 1994, an expert panel of the World Health Organisation recommended thresholds of bone mineral density in women to define osteoporosis [7–9] that have been widely, but not universally, accepted by the international scientific community and by regulatory agencies [10–12]. Osteoporosis in postmenopausal Caucasian women is defined as a value for bone mineral density (BMD) of >2.5 SD below the young average value, i.e. a *T*-score of ≤ 2.5 SD. Severe osteoporosis (established osteoporosis) uses the same threshold, but with one or more prior fragility fractures. The preferred site for diagnostic purposes are BMD measurements made at the hip, either at the total hip or the femoral neck [5]. For men, the same threshold as utilised for women is appropriate, since for any given BMD, the age adjusted fracture risk is more or less the same [13–16].

The diagnostic threshold identifies approximately 20% of postmenopausal women as having osteoporosis when measurements using dual energy X-ray absorptiometry (DXA) are made at the hip [7–9] (Table 1). The diagnostic use of the *T*-score cannot be used interchangeably with different techniques and at different sites, since the same *T*-score derived from different sites and techniques yields different information on fracture risk [17]. For example, in women at the age of 60 years the average *T*-score ranges from –0.7 to –2.5 SD, depending on the technique used [5,17]. Reasons include differences in the gradient of risk with which techniques predict fracture, discrepancies in the population standard deviation, and differences in the apparent rates of site-specific bone loss with age. A further problem is that inter-site correlations, although usually of statistical significance, are inadequate for predictive purposes in individuals giving rise to errors of mis-classification [18]. This does not mean that sites and techniques other than DXA at the hip cannot be used for risk assessment—only that the performance characteristics of the different techniques differ, and that less confusion arises when the *T*-score is reserved for diagnostic use with DXA at the hip.

Assessment of risk

The use of bone mass measurements for prognosis depends upon accuracy. Accuracy in this context is the ability of the measurement to predict fracture. In general, all absorptiometric techniques have high specificity but low sensitivity that varies with the cut-off chosen to designate high risk. Many cross-sectional and prospective population studies indicate that the risk for fracture increases by a factor of 1.4–2.6 for each standard deviation decrease in bone mineral density (Table 2) [19]. The ability of bone mineral density to predict fracture is comparable to the use of blood pressure to predict stroke, and substantially better than serum cholesterol to predict myocardial infarction [11,19,20]. Accuracy is improved by site-specific measurements (see Table 2), so that for forearm fractures, the risk might ideally be measured at the forearm, and for hip fracture, measurements made at the hip. In the immediate postmenopausal population, measurements at any site (hip, spine and wrist) predict any osteoporotic fracture equally well with a gradient of risk of approximately 1.5 per standard deviation decrease in bone mineral density.

The highest gradient of risk is found at the hip to predict hip fracture where the gradient of risk is 2.6. Thus, an individual with a *T*-score of –3 SD at the hip would have a 2.6^3 or greater than 15-fold higher risk than an individual with a *T*-score of 0 SD. By contrast, the same *T*-score at the spine would yield much lower risk estimate—approximately 4-fold increased (1.6^3). This emphasises the importance of accuracy or gradient of risk in the categorisation of fracture risk.

Table 2 Age-adjusted relative increase in risk of fracture (with 95% confidence interval) in women for every 1 SD decrease in bone mineral density (absorptiometry) below the mean value for age (from 19)

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

Despite these performance characteristics, it should be recognised that, just because bone mineral density is normal, there is no guarantee that a fracture will not occur—only that the risk is decreased. Indeed, most fractures will occur in patients without osteoporosis [7]. Conversely, if bone mineral density is in the osteoporotic range, then fractures are more likely, but not invariable. Consider, for example, the use of BMD at the age of 65 years and assume that the test predicts osteoporotic fractures (clinical spine, proximal humerus, hip and forearm fractures) with a gradient of risk of 2.0/SD change in BMD. At this age, the average 10-year probability of any one of these fractures is 12.4% [21]. If it were decided to target, say, 10% of the population at this age with the lowest BMD, 23% of fractures occurring over the next 10 years would be correctly identified by the test (i.e. sensitivity). Thus, 76% of all fractures would occur in women with a negative test [21]. The low sensitivity is one of the reasons why widespread population based screening is not widely recommended in women at the time of the menopause [7].

Fracture probability

Fracture risk is commonly expressed as a relative risk, but this has different meanings in different contexts. In the case of bone density measurements, gradients of risk are used, e.g. a 2.6-fold increase in hip fracture risk for each SD decrease in BMD. For dichotomous risk factors, risk is commonly expressed as the risk in individuals with a risk factor compared to the risk in those without the risk factor, or, as a risk compared with the general population. In order to compare risks, risk estimates need to be expressed in a standardised manner, e.g. as the risk relative to the population risk or as gradients of risk. Algorithms are now available for their conversion to be computed [21,22]. Nevertheless, the use of relative risks can be problematic. For example, at a given BMD, the relative risk of fracture decreases with age (since more of the population has osteoporosis) [22]. This is confusing for clinicians. For this and other reasons mentioned below, there has been interest in expressing risk in absolute terms, namely the probability or likelihood of fractures over a given period of time.

The absolute risk of fracture depends upon age and life expectancy as well as the current relative risk. In general, remaining lifetime risk of fracture increases with age up to the age of 70 years or so. Thereafter, probability plateaus and then decreases, since the risk of death with age outstrips the increasing incidence of fracture with age. Estimates of lifetime risk 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 assessing risk of individuals in whom treatment might be envisaged. Firstly, treatments are not presently given for a lifetime, due variably to side effects of continued treatment (e.g. hormone replacement treatment) or low continuance (most treatments). Moreover, the feasibility of life-long interventions has never been tested, either using high risk or global strategies. Secondly, the predictive value of low bone mineral density and some other risk factors for fracture risk may be attenuated over time [23]. Finally, the confidence in estimates decreases with time due to the uncertainties concerning future mortality trends [24]. For this reason, the IOF and the NOF recommend that risk of fracture should be expressed as a fixed-term absolute risk, i.e. probability over a 10-year interval [6]. The period of 10 years covers the likely duration of treatment and any benefits that may continue once treatment is stopped.

A further advantage of utilising fracture probability in risk assessment is that it standardizes the output from the multiple techniques and sites used for assessment. The estimated probability will, of course, depend upon the performance characteristics (gradient of risk) provided by any BMD technique at any one site. Moreover, it also permits the presence or absence of risk factors other than BMD to be incorporated with (or without) information on BMD as a single metric. This is important because there are many risk factors that give information over and above that provided by BMD. The most important of these is age.

Age and BMD

The same *T*-score with the same technique at any one site has a different significance at different ages. For any given *T*-score, fracture risk is much higher in the elderly than in the young [25]. This is because age contributes to risk independently of BMD. Indeed, from knowledge of the relationship between BMD and fracture risk, it would be predicted that hip fracture risk might increase 4-fold between the ages of 50 and 80 years. In reality, for hip fracture the risk increases 30-fold, indicating that over a lifetime, changes in age are approximately 7-fold more important than changes in BMD. It also indicates the independent value of assessing age.

The relationship between age, BMD and fracture probability at the spine and hip is given in Tables 3 and

4 [26]. At the threshold for osteoporosis (*T*-score = −2.5 SD), the 10-year probability of hip fracture ranges from 1.4 to 14.2% in men and women depending on age (see Table 3) [26]. Any difference in probability between men and women is not marked, since the same BMD at the hip carries a similar fracture risk in both sexes. The relationship between *T*-score and 10-year spine fracture probability is shown in Table 4 [26]. At the threshold of osteoporosis, there is approximately a 2-fold increase in probability with age between the ages of 50 and 85 years. As in the case of hip fracture, there is little difference in probabilities between men and women. For any given age, there is approximately a 4- to 5-fold increase in probability between a *T*-score of 0 and –2.5 SD. Thus, the consideration of age and BMD together increases the range of risk that can be identified. Imagine for the sake of argument that one wished to treat individuals with a greater than 10% 10-year probability of spine fracture, then very few individuals would be identified at the age of 50 years on the basis of BMD. The addition of age as a risk factor would, however, identify a substantial minority of individuals above this threshold risk. It is important to note that these data are applicable to individuals from Sweden. Hip fracture probabilities vary markedly around the world, much more than BMD, and fracture probabilities need to be calculated for each country.

Table 4 Ten-year probability of clinically apparent spine fracture in Swedish men and women by age and *T*-score at the femoral neck [26]

Age (years)	*T*-score						
	+1	0	−1	−2.0	−2.5	−3.0	−4.0
Men							
50	0.5	0.9	1.5	2.5	3.2	4.1	6.9
55	0.6	1.0	1.7	2.9	3.8	5.0	8.5
60	0.7	1.1	1.9	3.1	3.9	5.0	8.1
65	0.9	1.4	2.2	3.4	4.2	5.3	8.3
70	1.1	1.8	2.9	4.7	6.0	7.6	12.2
75	1.1	1.9	3.3	5.6	7.2	9.4	15.6
80	1.3	2.1	3.4	5.5	6.9	8.7	13.7
85	1.2	1.9	2.9	4.4	5.4	6.7	10.1
Women							
50	0.4	0.6	1.1	2.0	2.6	3.5	6.1
55	0.4	0.7	1.4	2.5	3.4	4.6	8.3
60	0.6	1.0	1.9	3.4	4.6	6.1	11.0
65	0.8	1.4	2.6	4.7	6.2	8.3	14.6
70	0.8	1.6	2.9	5.5	7.4	10.0	18.0
75	0.7	1.3	2.5	5.0	6.9	9.5	17.9
80	0.7	1.2	2.4	4.6	6.3	8.7	16.1
85	0.6	1.1	2.1	4.0	5.5	7.5	13.6

Other risk factors

A large number of additional risk factors for fracture have been identified. For the purposes of risk assessment in conjunction with a BMD test, interest lies in those factors that contribute significantly to fracture risk over and above that provided by bone mineral density measurements or age. Indeed, the consideration of such risk factors can be used to enhance a case finding strategy in osteoporosis by increasing the dynamic range of risk stratification. A caveat is that some risk factors are not amenable to particular treatments, so that the relationship between absolute probability of fracture and reversible risk is important for case-finding strategies. Liability to falls is an appropriate example where the risk of fracture is high, but treatment with agents affecting bone metabolism may have little effect on risk. Other risk factors such as prior fragility fractures contribute to a risk that is responsive to intervention.

Clinical risk factors

Many risk factors for osteoporotic fracture have been identified (Table 5) [27]. In general, risk factor scores show relatively poor specificity and sensitivity in predicting either bone mineral density or fracture risk [28–34]. Moreover, some risk factors vary in importance according to age. For example, risk factors for falling such as visual impairment, reduced mobility and treatment with sedatives, are more strongly predictive of fracture in the elderly than in younger individuals [35].

The choice of risk factor to use depends not only upon the concept of identifying reversible risk, but also on their ease of application. Many studies indicate for

Table 3 Ten-year probability of hip fracture in Swedish men and women according to age and BMD at the femoral neck [26]

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

Table 5 Risks for osteoporotic fractures [27]

Female gender	Premature menopause
Age[a]	Primary or secondary amenorrhoea
	Primary and secondary hypogonadism in men
Asian or Caucasian race	Previous fragility fracture[a]
Low BMD	Glucocorticoid therapy[a]
High bone turnover[a]	Family history of hip fracture[a]
Poor visual acuity[a]	Low body weight[a]
Neuromuscular disorders[a]	Cigarette smoking[a]
	Excessive alcohol consumption[a]
	Prolonged immobilisation
	Low dietary calcium intake
	Vitamin D deficiency

[a]These characteristics capture aspects of fracture risk over and above that provided by BMD

example that low intakes of calcium are a risk factor for hip fracture, but the quantification of calcium intake is not readily undertaken in general practice. A further consideration is the international validity. A series of recent meta-analyses from population-based cohorts has shown remarkable international consistency for low body mass index, a prior history of fracture, a family history of hip fracture, current smoking, high intake of alcohol and rheumatoid arthritis [36–41]. All provide information on fracture risk that is in part independent of BMD (Table 6).

Glucocorticoids are an important cause of osteoporosis and fractures [42,43]. Bone loss is believed to be most rapid in the first few months of treatment, and affects both axial and appendicular sites. Loss is most marked at the spine where cancellous bone predominates. The fracture risk conferred by the use of corticosteroids is, however, not solely dependent upon bone loss, and BMD independent risks have been identified (see Table 6) [37]. In this meta-analysis, the relative risk of hip fracture was increased 2.1- to 4.4-fold, depending upon age (higher at younger ages).

Many studies indicate that history of fragility fracture is an important risk factor for further fracture [44,45]. Fracture risk is approximately doubled in the presence of a prior fracture. The increase in risk is even more marked for a vertebral fracture following a previous spine fracture. For example, the presence of 2 or more prevalent vertebral fractures was associated with a 12-fold increase in fracture risk for any given bone mineral density [46]. A recent meta-analysis showing risks according to the site of a prior fracture is given in Table 7 [45]. These risks are not adjusted for BMD. In general, adjustment for BMD would decrease the relative risk by 10–20% (see Table 6) [4,36].

Low body mass index is a well recognised risk factor for fractures. The risk is most marked for lean individuals with a BMI of < 20 kg/m^2. Above 20 kg/m^2 increments in weight have little protective effect, so that leanness is the risk factor rather than obesity being a protective factor (see Table 6). The association of fracture risk with leanness is largely dependent on BMD. In the case of hip fracture risk, a modest risk persists after adjustment for BMD [40].

Smoking, high intakes of alcohol (> 2 units daily) and the ever use of corticosteroids provide risk indicators that are largely independent of BMD (see Table 6).

Biochemical assessment of fracture risk

Bone markers are increased after the menopause, and in several studies the rate of bone loss varies according to the marker value [46]. Thus, a potential clinical application of biochemical indices of skeletal metabolism is in assessing fracture risk. Prospective studies have shown an association of osteoporotic fracture with indices of bone turnover independent of bone mineral density in women at the time of the menopause and elderly women [48–50]. In elderly women with values for resorption markers exceeding the reference range for premenopausal women, fracture risk is increased approximately 2-fold after adjusting for bone mineral density. These studies suggest that a combined approach using bone mineral density with indices of bone turnover may improve fracture prediction in postmenopausal women [51].

Integrating risk factors

How can the combined intelligence of the presence or absence of risk factors, BMD and age be factored into estimates of fracture probability? The general

Table 6 Risk ratio for hip fracture associated with risk factors adjusted for age, with and without adjustment for BMD

Risk indicator		Without BMD		With BMD	
		RR	95% CI	RR	95% CI
Body mass index	(20 vs 25 kg/m^2)	1.95	1.71–2.22	1.42	1.23–1.65
	(30 vs 25 kg/m^2)	0.83	0.69–0.99	1.00	0.82–1.21
Prior fracture after 50 years		1.85	1.58–2.17	1.62	1.30–2.01
Parental history of hip fracture		2.27	1.47–3.49	2.28	1.48–3.51
Current smoking		1.84	1.52–2.22	1.60	1.27–2.02
Ever use of systemic corticosteroids		2.31	1.67–3.20	2.25	1.60–3.15
Alcohol intake > 2 units daily		1.68	1.19–2.36	1.70	1.20–2.42
Rheumatoid arthritis		1.95	1.11–3.42	1.73	0.94–3.20

Table 7 Meta-analysis of the risk of fracture in women with a prior fracture at the sites shown (adapted from [43])

Site of prior	Risk of subsequent fracture at			
Fracture	Hip	Spine	Forearm	Minor fracture
Hip	2.3	2.5	1.4	1.9
Spine	2.3	4.4	1.4	1.8
Forearm	1.9	1.7	3.3	2.4
Minor fracture	2.0	1.9	1.8	1.9

relationship between relative risk and 10-year probability of hip and other fractures is shown in Table 8 [21]. For example, a woman at the age of 60 years has on average a 10-year probability of hip fracture of 2.4% (see Table 8). In the presence of a prior fragility fracture this risk is increased approximately 2-fold and the probability increases to 4.8%. The integration of risk factors is not new and has been successfully applied in the management of coronary heart disease [51].

There are, however, a number of problems to be resolved before combinations of apparently independent risk factors can be utilised. Although corticosteroid treatment confers a risk over and above that afforded by age and BMD, as does a prior fragility fracture, the relationship between corticosteroid use and prior fragility fracture has not yet been explored. Until these interrelationships are established and validated on an international basis, the use of multiple risk factors must be cautiously applied.

Table 8 Ten-year probability of fracture in men and women from Sweden according to age and the risk (*RR*) relative to the average population [21]

RR	Age (years)			
	50	60	70	80
Hip fracture				
Men				
1	0.8	1.3	3.7	9.5
2	1.7	2.5	7.2	17.9
3	2.5	3.7	10.6	25.3
4	3.3	4.9	13.8	31.8
Women				
1	0.6	2.4	7.9	18.0
2	1.1	4.8	15.1	32.0
3	1.7	7.0	21.7	42.9
4	2.3	9.3	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

Intervention thresholds

Of all osteoporotic fractures, hip fracture confers the greatest morbidity and economic consequences and has been the subject of much research. When hip fracture alone is considered, a 10-year probability of 10% or more provides a cost effective threshold for women in Sweden [52]. However, many fractures other than hip fracture also contribute to morbidity, particularly in the young, in whom hip fractures are rare. An approach to integrating all osteoporotic fractures is to weight the incidence of osteoporotic fractures at different ages according to their morbidity assessed as disutility (i.e. the cumulative loss in quality of life). For example, in terms of disutility, two vertebral fractures might equate to one hip fracture [53]. When the incidence by age is weighted in this way the morbidity from osteoporotic fractures at the age of 50 years is approximately 5-fold greater than that due to hip fracture at this age. Conversely, at the age of 80 years the ratio is approximately 1.2. On the assumption that the ratio between morbidity from hip fracture and from other fractures is similar to the costs of hip fracture and other fractures, intervention thresholds can be established on the basis of cost utility [54]. When hip fracture alone is considered, a 10-year hip fracture probability of 10% or more is a cost effective threshold for women in Sweden or the UK. When account is taken of other fractures, the threshold for hip fracture probability at which interventions become cost effective decreases, particularly in younger individuals (Table 9) [55]. For example, at the age of 50 years the 10-year probability of hip fracture at which intervention becomes cost-effective is 1.1 (equivalent to a relative risk of 3.8). The reason that the threshold probability is lower at younger ages is that many fractures other than hip fractures are contributing to the calculation of cost-effectiveness. In other words, hip fracture probability is being used as a risk indicator that takes account of the costs and consequences of the complete range of fracture outcomes at any given age. These thresholds for intervention correspond to a BMD value that lies between –2 and –3 SD over all ages (in the absence of other risk factors) (Fig. 1) [27].

Table 9 Ten-year hip fracture probability (%) according to age and risk relative to the general female population from the UK at which intervention is cost-effective (from [53])

Age (years)	RR	Probability (%)
50	3.8	1.10
55	2.6	1.81
60	1.9	2.64
65	1.4	3.70
70	1.1	5.24
75	0.9	6.87
80	7.8	8.52
85	0.6	8.99
90	0.5	7.12

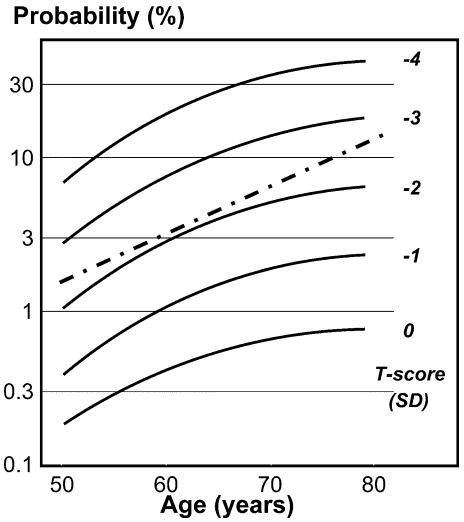

Fig. 1 Ten-year probability of hip fracture in Swedish women according to *T*-scores assessed at the femoral neck by DXA. The *diagonal dotted lines* denote the probability at which interventions are cost effective (from [27])

Optimisation of a case finding strategy

It is evident that the consideration of multiple risk factors improves risk stratification of individuals and thereby enhances a case-finding strategy. The interrelationship between BMD, age and a single independent clinical risk factor is now established, though the relationship between all the clinical risk factors has yet to be formalised. It is likely, however, that the risk conferred by the combination of several independent clinical risk factors would be sufficiently high that it exceeds an intervention threshold.

These considerations suggest that a BMD test may not be required in all individuals who are offered treatment. The value of pharmacological agents in decreasing fracture risk has been best quantified in those identified on the basis of low BMD. Indeed, for some interventions, treatment of individuals without osteoporosis may yield less in terms of fracture dividends, but in other studies, individuals with osteopenia respond to treatment with the same relative risk reduction. In this regard, the question arises whether patients identified on the basis of clinical risk factors alone have a risk identified that would be amenable to therapeutic manipulation. Although risk factors such as a prior fragility fracture are "independent" of BMD, they are not totally independent in the sense that patients, for example, identified on the basis of fragility fracture, do have low BMD. Indeed, patients selected only on the basis of fracture have been shown to respond to therapeutic intervention with bisphosphonates [56]. Thus, individuals selected on the basis of clinical risk factors are likely to have a low BMD. The same holds true for many other clinical risk factors.

If this assumption is accepted, then the following strategy can be envisaged. The first step is an assessment of fracture probability that is based solely on clinical risk factors. This is expected to identify three groups of individuals. The first are those at very high risk above an intervention threshold in whom a BMD test would not alter their classification. These patients can be offered treatment irrespective of BMD. In practice, BMD might be measured, say at the lumbar spine, so that response to treatment can be monitored.

A second group comprises individuals who on the basis of clinical risk factor assessment have a very low probability of osteoporotic fracture, so low that the estimate of BMD would not alter their stratification to be above a given level of risk. An intermediate group are those in whom fracture probability is close to an intervention threshold where the probability is high that a BMD test might re-categorise individuals at high to low risk (or vice versa). The formalisation of this approach is not yet complete, but preliminary evidence from a variety of prospectively studied cohorts suggests that a minority of individuals would require a BMD test on this basis [57].

Conclusions

The diagnosis of osteoporosis centres on the assessment of bone mineral density at the hip using DXA. However, other sites and validated techniques can be used for fracture prediction. Several clinical risk factors contribute to fracture risk, in part independently of BMD. These include age, prior fragility fracture, premature menopause, a family history of hip fracture and the use of oral corticosteroids. Since several of these risk factors are partly dependent on BMD, their use in conjunction with BMD improves sensitivity of fracture prediction without adverse effects on specificity.

In the absence of validated population screening strategies, a case finding strategy can be developed based on the assessment of fracture probability utilising clinical risk factors, and where appropriate additional testing such as BMD. Because of the multiple techniques available for fracture risk assessment, and the multiple fracture outcomes, the desirable measurement to determine intervention thresholds is 10-year probability of fracture. Many treatments can be given cost effectively to men and women where hip fracture probability over 10 years ranges from 1 to 10% depending on age.

References

1. Anonymous (1993) Consensus development conference: diagnosis, prophylaxis and treatment of osteoporosis. Am J Med 94:646–650
2. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D, on behalf of the European Foundation for Osteoporosis and Bone Disease (1997) Guidelines for diagnosis and management of osteoporosis. Osteoporos Int 7:390–406
3. Royal College of Physicians (1999) Clinical guidelines for the prevention and treatment of osteoporosis. RCP, London

4. National Osteoporosis Foundation (1998) Analyses of the effectiveness and cost of screening and treatment strategies for osteoporosis: a basis for development of practice guidelines. Osteoporos Int 8 (suppl 4):1–88
5. Kanis JA, Glüer CC for the Committee of Scientific Advisors, International Osteoporosis Foundation (2000) An update on the diagnosis and assessment of osteoporosis with densitometry. Osteoporos Int 11:192–202
6. Kanis JA, Black D, Cooper C, Dargent P, Dawson-Hughes B, De Laet C et al. (2002) A new approach to the development of assessment guidelines for osteoporosis. Osteoporos Int 13:527–536
7. World Health Organisation (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Technical Report Series 843. WHO, Geneva
8. Kanis JA, Melton LJ, Christiansen C, Johnston CC, Khaltaev N (1994) The diagnosis of osteoporosis. J Bone Miner Res 9:17–1141
9. Kanis JA, Johnell O, Oden A, Jonsson B, De Laet C, Dawson A (2000) Risk of hip fracture according to the World Health Organization criteria for osteoporosis and osteopenia. Bone 27:585–590
10. Committee for Proprietary Medicinal Products (CPMP) (1997) Note for guidance on involutional osteoporosis in women. European Agency for the Evaluation of Medicinal Products, London (CPMP/EWP/552/95)
11. World Health Organisation (1998) Guidelines for preclinical evaluation and clinical trials in osteoporosis. WHO, Geneva
12. Liu, Z, Piao J, Pang L, Qing X et al. (2002) The diagnostic criteria for primary osteoporosis and the incidence of osteoporosis in China. J Bone Miner Metab 20:181–189
13. Kanis JA, Johnell O, Oden A, De Laet C, Mellstrom D (2001) Diagnosis of osteoporosis and fracture threshold in men. Calcif Tissue Int 69:218–221
14. DeLaet CEDH, Van Hout BA, Burger H, Hofman A, Weel AEAM, Pols HAP (1998) Hip fracture prediction in elderly men and women: validation in the Rotterdam Study. J Bone Miner Res 13:1587–1593
15. Ross P, Huang C, Davis J, Imose K, Yates J, Vogel J, Wasnich R (1995) Predicting vertebral deformity using bone densitometry at various skeletal sites and calcaneous ultrasound. Bone 16:325–332
16. Lunt M, Felsenberg D, Reeve J, Benevolenskaya L, Cannata J, Dequeker J (1997) Bone density variation and its effect on risk of vertebral deformity in men and women studied in thirteen European Centres: the EVOS Study. J Bone Miner Res 12:1883–1894
17. Faulkner KG, von Stetten E, Miller P (1999) Discordance in patient classification using *T*-scores. J Clin Densitom 2:343–350
18. Arlot ME, Sornay-Rendu E, Garnero P, Vey-Marty B, Delmas PD (1997) Apparent pre- and postmenopausal bone loss evaluated by DXA at different skeletal sites in women: the OFELY cohort. J Bone Miner Res 12:683–690
19. Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 312:1254–1259
20. Cooper C, Aihie A (1994) Osteoporosis: recent advances in pathogenesis and treatment. Q J Med 87:203–209
21. Kanis JA, Johnell O, Oden A, De Laet C, Jonsson B, Dawson A (2001) Ten year risk of osteoporotic fracture and the effect of risk factors on screening strategies. Bone 30:251–258
22. Kanis JA, Johnell O, Oden A, Jonsson B, Dawson A, Dere W (2000) Risk of hip fracture in Sweden according to relative risk: an analysis applied to the population of Sweden. Osteoporos Int 11:120–127
23. Kanis JA, Johnell O, Oden A, Jonsson B, DeLaet C, Dawson A (2000) Prediction of fracture from low bone mineral density measurements overestimates risk. Bone 26:387–391
24. Oden A, Dawson A, Dere W, Johnell O, Jonsson B, Kanis JA (1999) Lifetime risk of hip fracture is underestimated. Osteoporos Int 8:599–603
25. Hui SL, Slemenda CW, Johnston CC (1988) Age and bone mass as predictors of fracture in a prospective study. J Clin Invest 81:1804–1809
26. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B (2001) Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int 12:989–995
27. Kanis JA (2002) Diagnosis of osteoporosis and assessment of fracture risk. Lancet 359:1929–1936
28. Johnell O, Gullberg B, Kanis JA et al. (1995) Risk factors for hip fracture in European women: the MEDOS Study. J Bone Miner Res 10:1802–1815
29. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, Vogt TM (1995) Risk factors for hip fracture in white women. N Engl J Med 332:767–773
30. Compston JE (1992) Risk factors for osteoporosis. Clin Endocrinol 36:223–224
31. Ribot C, Pouilles JM, Bonneu M, Tremollieres F (1992) Assessment of the risk of postmenopausal osteoporosis using clinical risk factors. Clin Endocrinol 36:225–228
32. Kanis JA, Johnell O, Gullberg B, Allander A, Elffors L, Dequeker J et al. (1999) Risk factors for hip fracture in European men. The MEDOS study. Osteoporos Int 9:45–54
33. Nguyen T, Sambrook SP, Kelly P, Jones G, Freund J, Eisman J (1993) Prediction of osteoporotic fractures by postural instability and bone density. BMJ 307:1111–1115
34. Poor G, Atkinson EJ, O'Fallon WM, Melton LJ III (1995) Predictors of hip fractures in elderly men. J Bone Miner Res 10:1900–1907
35. Kanis JA, McCloskey EV (1996) Evaluation of the risk of hip fracture. Bone 18:127–132
36. Kanis JA, De Laet C, Delmas P, Garnero P, Johansson H, Johnell O, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Oden A, Pols H, Reeve J, Silman A, Tenenhouse A (2004) A meta-analysis of previous fracture and fracture risk. Bone 35:375–382
37. Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Melton LJ, Tenenhouse A, Reeve J, Silman AJ, Pols HAP, Eisman JA, McCloskey EV, Mellstrom D (2004) A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 19:893–899
38. Kanis JA, Johnell O, Oden A, Johansson H, De Laet C, Eisman JA, Fujiwara S, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman AJ, Tenenhouse A (2004) Smoking and fracture risk: a meta-analysis. Osteoporos Int (in press)
39. Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Eisman JA, McCloskey EV, Mellstrom D, Melton LJ, Pols HAP, Reeve J, Silman AJ, Tenenhouse A (2004) A family history of fracture and fracture risk: a meta-analysis. Bone (in press)
40. De Laet C, Kanis JA, Oden A, Johansson H, Johnell O, Delmas P et al. (2004) Body mass index as a predictor of fracture risk: A meta-analysis. Osteoporos Int (in press)
41. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A (2004) Alcohol intake as a risk factor for fracture. Osteoporos Int (in press)
42. Van Staa TP, Leufkens HGM, Abenhaim L, Zhang B, Cooper C (2001) Use of oral corticosteroids and risk of fractures. J Bone Miner Res 15:993–1000
43. Van Staa TP, Leufkens HGM, Cooper C (2002) The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 13:777–787
44. Klotzbuecher CM, Ross PD, Landsman PB, Abbot TA, Berger M (2000) Patients with prior fractures have increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 15:721–727
45. Ross PD, Genant HK, Davis JW, Miller PD, Wasnich RD (1993) Predicting vertebral fracture incidence from prevalent fractures and bone density among non black, osteoporotic women. Osteoporos Int 3:120–126

46. Delmas PD (ed) (2000) The use of biochemical markers of bone turnover in the management of post-menopausal osteoporosis. Osteoporosis Int 11:S1–S76
47. Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD (2000) Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women. The Ofely study. J Bone Miner Res 15:1526–1536
48. Garnero P, Hauser E, Chapuy MC, Marcelli C, Grandjean H, Muller C, Cormier C, Breard G, Meunier PJ, Delmas PD (1996) Markers of bone turnover predict hip fractures in elderly women. The EPIDOS prospective study. J Bone Miner Res 11:1531–1538
49. Hansen M, Overgaard K, Riis B, Christiansen C (1991) Role of peak bone mass and bone loss in postmenopausal osteoporosis: 12 year study. BMJ 303:961–964
50. Johnell O, Oden A, DeLaet C, Garnero P, Delmas PD, Kanis JA (2002) Biochemical indices of bone turnover and the assessment of fracture probability. Osteoporos Int 13:523–526
51. Dyslipidaemia Advisory Group on behalf of the Scientific Committee of the National Heart Foundation of New Zealand (1996) National Heart Foundation Clinical Guidelines for the assessment and management of dyslipidaemia. N Z Med J 109:224–232
52. Kanis JA, Dawson A, Oden A, Johnell O, De Laet C, Jonsson B (2001) Cost-effectiveness of preventing hip fracture in the general female population. Osteoporos Int 12:356–361
53. Kanis JA, Johnell O, Oden A, Borgstrom F, Zethraeus N, De Laet C, Jonsson B (2004) The risk and burden of vertebral fractures in Sweden. Osteoporos Int 15:20–26
54. Kanis JA, Oden A, Johnell O, Jonsson B, De Laet C, Dawson A (2001) The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int 12:417–427
55. Kanis JA, Johnell O, Oden A, De Laet C, Oglesby A, Jonsson B (2002) Intervention thresholds for osteoporosis. Bone 13:26–31
56. Kanis JA, Barton IP, Johnell O (2004) Risedronate decreases fracture risk in patients selected solely on the basis of prior vertebral fracture. Osteoporos Int (in press)
57. Johansson H, Oden A, Johnell O, Jonsson B, De Laet C, Oglesby A, McCloskey EV, Kayan K, Jalava T, Kanis JA (2004) Optimisation of BMD measurements to identify high risk groups for treatment—a test analysis. J Bone Miner Res 19:906–913