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Assessing the Risk of Vertebral Osteoporosis

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ABSTRACT

Assessment of osteoporosis includes an accurate diagnosis, a consideration of the differential diagnosis, and prognostic assessment. Diagnosis of osteoporosis is based on bone mineral density (BMD) measurements and is defined as a BMD value that is 2.5 standard deviations or more below the average value in young healthy women (T score ≤-2.5 SD). Established osteoporosis is defined as a T-score of ≤-2.5 SD in the presence of a prior fragility fracture.

The assessment of prognosis is important for defining intervention thresholds. Future fracture risk depends not only on BMD, but also on age. In addition, a variety of risk factors have been identified that increase fracture risk over and above that provided by BMD and age. Of particular importance is a prior fragility fracture, low body mass index and use of corticosteroids. The combination of independent risk factors permits a more accurate stratification of risk so that more patients at high risk can be identified.

Risk of future fracture is optimally expressed as a probability. Ten-year fracture probabilities are appropriate for clinical use. The impact of BMD, age and other risks on fracture probability have recently been determined and provide a mechanism for optimising assessment of patients so that treatments can be efficiently directed to those most in need.

Keywords: Vertebral fracture, Fracture probability, Diagnosis, Prognosis

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INTRODUCTION

Vertebral fractures form an integral component of the osteoporotic syndrome. Indeed, the majority of intervention studies have focused on the effectiveness of pharmacological agents to reduce the burden of vertebral fractures. There are a number of problems to consider in the assessment of vertebral fracture. Most fractures are clinically obvious and give rise to morbidity, but in the case of vertebral fractures a proportion may not come to clinical attention. The uncertainty arises in defining the presence or absence of fractures. There is no general agreement on the criteria for the radiographic definition of vertebral fracture, and it is generally diagnosed as a change in vertebral shape. Thus, the incidence and prevalence of vertebral fracture depends critically upon the methodology used. The incidence of symptomatic fractures is markedly lower than that judged by radiographic criteria alone. A further problem is that the major clinical manifestation of established vertebral osteoporosis is back pain, but this is non-specific. Indeed, back pain is so common that at least up to old age it is more likely when present to be due to other reasons[1].

The assessment of vertebral osteoporosis includes accurate diagnosis and a consideration of the differential diagnosis. Both these topics are dealt with elsewhere[2]. A further consideration is the prognosis or risk assessment. Where the risk of further fractures is high, intervention should be considered. This paper briefly reviews the prognostic assessment in the context of vertebral osteoporosis.

DIAGNOSIS OF OSTEOPOROSIS

The internationally agreed definition of osteoporosis is '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'[3]. The definition of osteoporosis captures the notion that low bone mass is an important component of the risk of fracture, but that other abnormalities occur in the skeleton, and that non-skeletal factors such as falls are also important. Nevertheless, it is only bone mass measured as bone mineral density (BMD) that can be presently measured with precision and accuracy, and its measurement forms the basis for the diagnosis of osteoporosis.

For diagnostic purposes two thresholds of bone mineral density have been proposed for Caucasian women based on the T-score[4,5]. The first defines the majority of individuals who will sustain a fracture in the future (osteoporosis), and the second a higher

threshold that may be more appropriate for investigating the impact of strategies to prevent bone loss in women at the time of the menopause (low bone mass; osteopenia). Osteoporosis denotes a value for bone mineral density that is 2½ standard deviations (SD) or more below the young adult mean value (T-score <-2.5 SD). Low bone mass denotes a T-score that lies between -1 and -2.5 SD. Severe or 'established' osteoporosis denotes osteoporosis as defined above in the presence of one or more documented fragility fractures usually of the wrist, spine or hip.

Despite the widespread acceptance of the T-score for diagnostic criteria, several problems have emerged in its practical use. The criteria were established largely for descriptive purposes, but it has also been widely advocated as an intervention threshold. Although this may prove to be appropriate, the same T-score has a quite different significance in men or women at different ages. For example, a T-score of -2.5 SD at the femoral neck in women from Sweden carries a 10-year spine fracture probability of 3.8% at the age of 50 years but a 10% risk at the age of 70 years[6]. A further problem is the profusion of techniques and sites available for assessment. Bone mineral assessment at one site is a poor predictor of mineral status at another site, due to biological variation in skeletal composition and intrinsic errors of accuracy[7]. Also, the T-score at one site is of even less value in predicting the T-score at another. Additional reasons include differences in population variance (used to compute the T-score) and differences in sensitivity to detect changes. Indeed, if the T-score were to be used with different techniques, the prevalence of osteoporosis and the proportion of individuals would vary so much[8] as to devalue the credibility of any diagnostic approach with T-scores (Table I).

For these reasons it is preferred to use a standardised site for diagnosis. The site recommended is the hip, since measurements at the hip predict hip fractures more efficiently than at other sites and the site is less prone to inaccuracies from co-existing osteoarthrosis[7]. The normative data recommended is that derived from a large population sample in the USA[9]. The same cut-off value for women (0.577 g/cm^2 at the femoral neck) can be used in men, since the same BMD carries approximately equal fracture risks in both sexes[10]. The prevalence of osteoporosis in Sweden is approximately 20% in women and 6% in men above the age of 50 years (Table II)[11].

This does not mean to say that other techniques and other sites cannot be used for risk assessment. However, their prognostic significance differs from that provided from bone mineral density measurements made at the hip.

Table I. Estimates of T-scores and the prevalence of osteoporosis according to side and technique.

Measurement site	Technique	T-score at 60 years	WHO classification	Prevalence of osteoporosis (%)
Spine	QCT	-2.5	OP	50
Spine	Lateral DXA	-2.2	LBM	38
Spine	DXA	-1.3	LBM	14
Forearm	DXA	-1.4	LBM	12
Heel	Achilles	-1.5	LBM	11
Total hip	DXA	-0.9	N	6
Heel	Sahara	-0.7	N	3

OP = osteoporosis; LBM = low bone mass: N = normal. (from reference 8 and manufacturer's data).

Table II. Prevalence of osteoporosis at the age intervals shown in men and women from Sweden[11].

Age range (years)	Percent of men population	Number affected (000)	Percent of women population	Number affected (000)
50-54	2.5	7.0	6.3	17.0
55-59	3.5	7.6	9.6	21.1
60-64	5.8	11.4	14.3	30.0
65-69	7.4	14.2	20.2	43.7
70-74	7.8	14.6	27.9	63.0
75-79	10.3	13.7	37.5	68.3
80-84	16.6	14.7	47.2	67.8
50-84	6.3	83.2	21.2	310.9

Table III. Incidence (rate/1,000/year) of clinical vertebral fracture by age and sex in Malmo, Sweden. The left hand columns give incidence in the unselected population and the right hand columns the incidence of a first fracture[13].

Age range (years)	Any vertebral fracture		First vertebral fracture	
	Men	Women	Men	Women
50-54	1.95	1.61	1.35	1.17
55-59	1.19	1.58	1.02	1.27
60-64	2.26	3.03	1.91	2.12
65-69	2.42	4.39	1.73	3.29
70-74	4.99	7.78	2.85	5.83
75-79	6.19	11.11	4.95	7.61
80-84	9.33	11.63	5.60	7.70
50-84	11.94	16.41	11.08	12.63

THE INCIDENCE OF VERTEBRAL FRACTURE

As mentioned, there are problems in defining vertebral fracture. A clinical definition is appropriate in many settings, but fracture diagnosed solely on radiographs are associated with significant morbidity[12]. They are also an important risk factor for future fractures. There have been few prospective

Table IV. Relative risk of fracture at the sites shown according to the site of a prior fracture (adapted from 15).

Site of prior fracture	Site of subsequent fracture									
	Distal forearm		Spine		Proximal humerus[c]		Hip		Pooled	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Forearm	3.0	2.0-5.3	1.7	1.4-2.1	2.4	1.7-3.4	1.9	1.6-2.2	2.0	1.7-2.4
Spine	1.4	1.2-1.7	4.4	3.6-5.4	1.8	1.7-1.9	2.3	2.0-2.8	1.9	1.7-2.3
Humerus[c]	1.8	1.3-2.4	1.9	1.3-2.8	1.9	1.3-2.7	2.0	1.7-2.3	1.9	1.7-2.2
Hip	1.4	-[a]	2.5	1.8-3.5	1.9	-[b]	2.3	1.5-3.7	2.4	1.9-3.2
Pooled	1.9	1.3-2.8	2.0	1.6-2.4	1.9	1.6-2.2	2.0	1.9-2.2	2.0	1.8-2.1

[a] No studies
[b] One study
[c] Assumed to be equivalent to a 'minor fracture' from the meta-analysis

studies of the incidence of vertebral fracture. In Sweden the incidence rises with age in both sexes, though more markedly in women than in men. At the age of 50 years rates are higher in men than women, presumed to be due to higher trauma rather than lower fraility (Table III)[13]. It is also important to recognise that individuals may have more than one vertebral fracture. When assessing risk in an individual without fracture, it is important to know the risk of a first vertebral fracture.

The incidence of vertebral fracture is much higher using morphometric criteria to diagnose fractures, since many do not come to clinical attention. Indeed, clinical fractures account for approximately 25% of the burden of all deformities in women and about 50% in the case of men.

RISK FACTORS FOR VERTEBRAL FRACTURE

A large number of risk factors have been identified for vertebral osteoporotic fractures. Strong risk factors include age, low body mass index, a maternal history of fracture, prior fragility fractures, use of corticosteroids and in particular low BMD. Many prospective studies have shown that BMD measurements provide prognostic information on vertebral fracture risk[4,14]. A recent meta-analysis estimates that the risk of vertebral fracture is increased 1.8-fold for each standard deviation decrease in BMD at the femoral neck. Prognostic assessment is improved by measuring the site of biological relevance (the spine). Spine bone mineral density measurements are associated with a 2.3-fold increase in risk for each standard deviation decrease in bone mineral density[14]. BMD measurements are at least as good for predicting hip fracture as blood pressure measurements are for predicting stroke, and considerably better than cholesterol measurements for predicting myocardial infarction in men[4,14].

A particularly strong risk factor for vertebral fracture is a prior vertebral fracture. The risk of future fractures is approximately twice that of individuals without fractures at most sites but is increased more than four-fold at another vertebral site[15] (Table IV).

In addition to age, prior fractures and BMD, a number of other factors contribute to fracture risk. Examples include attenuation of ultrasound, biochemical estimates of skeletal turnover, smoking and low body mass index. Other factors include premature menopause, certain diseases such as dementia and drugs such as the corticosteroids and major tranquilisers.

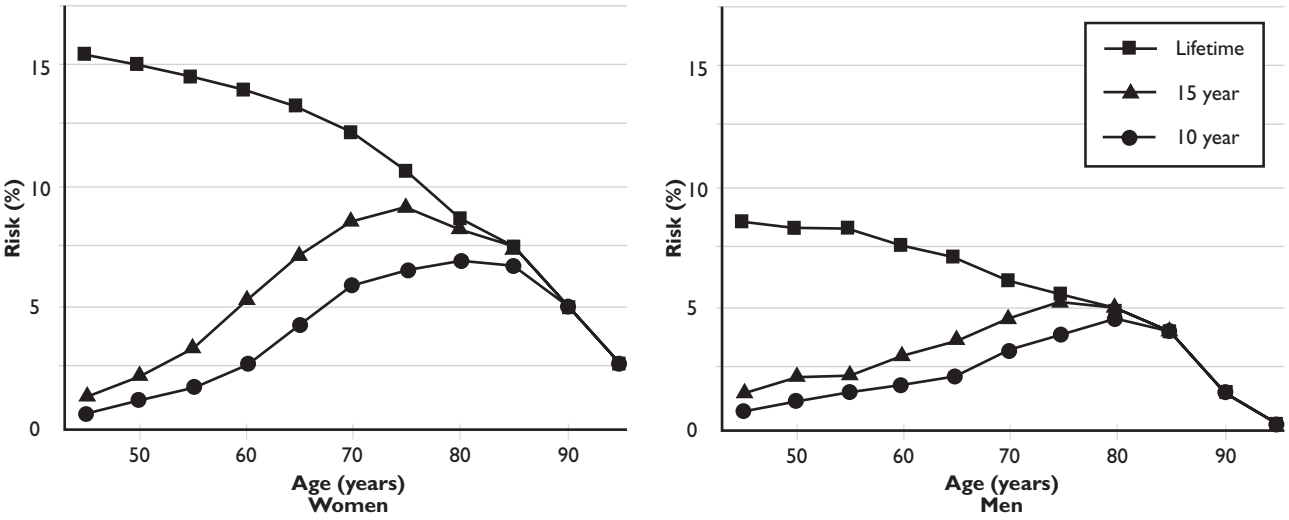
Many of these risk factors are independent of age and BMD. For example, a prior fracture increases the risk of a future fracture even after adjustment for age and BMD. The same is true of family history, high biochemical estimates of bone turnover, corticosteroid use and in some populations, smoking and low body mass index. The importance of this for clinical assessment is marked. For example, women at the threshold for osteoporosis aged 50 years have a 2.9-fold higher risk of hip fracture than the general population of the same age[16]. In the presence of a prior fracture the risk is increased approximately five-fold. Thus, the combination of risk factors improves the sensitivity of assessment, ie the detection rate of individuals who will fracture[16,17].

The consideration of multiple risk factors is commonly used for other multifactorial disorders such as cardiovascular diseases[18]. The consideration of smoking, blood pressure, diabetes and serum cholesterol permits the identification of patients at high risk, whereas the use of serum cholesterol alone has a low gradient of risk, significantly poorer than the assessment of BMD alone to predict vertebral fracture[14]. The future of osteoporosis is likely to include a similar approach to optimise case-finding strategies.

ASSESSMENT OF RISK

The risk of future vertebral fractures is optimally expressed as absolute risk, i.e. probability. For example,

Fig. 1 Risk of a first vertebral fracture in men and women by age. Risks are shown as lifetime, 15-years or 10-years probabilities.



what are the probabilities that an individual under given circumstances will sustain a fragility fracture in the future. This demands knowledge of the incidence of first fracture, and for long-term prediction also the mortality risk. Such data are available for Sweden. For example, at the age of 50 years the remaining lifetime risk of a clinical spine fracture is 15. 1% in women and 8.3% in men[13]. The lifetime risk of other common osteoporotic fractures is shown in Table V. Lifetime risk decreases progressively with age since, although the incidence rises with age, the increase in incidence is less than the increase in mortality (Fig. 1).

Estimates for lifetime risk are of value in considering the future burden of osteoporosis in the community and the effects of intervention strategies. They are less important for assessing risk to individuals in whom treatment might be envisaged. This is because treatments are not presently given for a lifetime, due variably to side effects of continued treatment (e.g. hormone replacement therapy) or low continuance (most treatments). Moreover, the feasibility of lifelong interventions has never been tested using high risk or global strategies[19]. For the purposes of assessment in individuals a ten-year time frame is more suitable. This covers the three to five years or so where the effectiveness of treatments has been well tested, and also takes account of the offset time, the duration of time that benefits continue when treatment is stopped. Ten-year probability of vertebral fracture increases with age in both men and women up to the age of approximately 80 years (see Fig. 1). Thereafter, these risks decline since in the elderly the 10-year mortality risk exceeds the fracture risk.

Risk prediction can be more accurately quantified following assessment with BMD. Ten-year risk

Table V. Remaining lifetime risk of fracture (%) in men and women from Malmo, Sweden at the ages shown[13].

Type of fracture	At 50 years			At 80 years		
	Men	Women	Risk ratio	Men	Women	Risk ratio
Forearm	4.6	20.8	4.5	1.6	8.9	5.6
Hip	10.7	22.9	2.1	9.1	19.3	2.1
Spine	8.3	15.1	1.8	4.7	8.7	1.9
Proximal Humerus	4.1	12.9	3.1	2.5	7.7	3.1
Any of these	22.4	46.4	2.1	15.3	31.7	2.1

Table VI. Ten year probability of spine fracture in men and women from Sweden according to age and T-score[6].

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

Table VII. Ten-year probability of vertebral fracture in women by age and diagnostic category according to the T-score in men and women from Sweden. Probabilities are shown for each age for all individuals below the average value for BMD and the thresholds for osteopenia and osteoporosis[6].

Age (years)	<0	<-1	<-2.5
45	0.8	1.1	2.1
50	1.4	1.9	3.5
55	1.9	2.5	4.6
60	2.9	3.6	6.4
65	4.5	5.3	9.0
70	6.0	6.7	10.9
75	6.4	6.9	10.7
80	6.8	7.1	10.2
85	6.7	6.9	9.4

Table VIII. Ten year probability (%) of spine fracture in men and women from Sweden according to relative risk at the age shown[17].

RR	50	55	60	65	70	75	80	85
Men								
1.0	1.5	1.7	2.2	3.2	4.6	5.5	6.3	4.2
2.0	3.1	3.3	4.3	6.3	8.9	10.6	12.1	8.2
3.0	4.5	4.9	6.4	9.3	13.0	15.4	17.5	12.0
4.0	6.0	6.4	8.4	12.2	16.9	19.9	22.4	15.6
5.0	7.5	8.0	10.4	15.0	20.5	24.1	26.9	19.0
6.0	8.9	9.5	12.4	17.7	24.0	28.0	31.0	22.2
Women								
1.0	1.6	2.2	3.5	5.5	8.1	9.0	9.3	8.8
2.0	3.1	4.4	6.9	10.8	15.5	17.2	17.6	16.5
3.0	4.6	6.5	10.2	15.7	22.3	24.5	25.0	23.4
4.0	6.1	8.6	13.3	20.3	28.4	31.1	31.1	29.6
5.0	7.6	10.7	16.4	24.7	34.0	37.0	37.3	35.1
6.0	9.0	12.7	19.3	28.8	39.2	42.3	42.5	40.0

Table IX. Comparison of life expectancy, hip fracture incidence and hip fracture probability in men and women from Singapore and Sweden[20].

	Singapore		Sweden	
	Men	Women	Men	Women
Life expectancy (years)				
AT the age of 50 years	27.6	31.9	28.5	32.8
At the age of 75 years	10.5	12.7	9.3	12.2
Hip fracture incidence (rate/100,000)[a]				
Between the age of				
50-54 years	26 (22)	12 (14)	21	41
60-64 years	50 (49)	54 (81)	111	156
70-74 years	238 (210)	384 (408)	347	594
Probability of hip fracture (%)				
10 years from the age of				
50 years	0.3	0.2	0.5	0.6
60 years	0.7	1.3	1.5	2.2
70 years	3.0 (3.1)	6.7 (7.3)	3.9	7.1
80 years			9.1	17.7

[a] Hip fracture rates from Koh et al[21] and Lau et al[22] in parentheses.

according to T-score is given in Table VI[6]. It is important to note that 10-year probability of vertebral fracture varies both according to age and T-score. Thus, for a given T-score, 10-year probability increases with age. This is one of the reasons why the T-score alone is unhelpful for risk assessment. It is also important to note that a population of osteoporotic patients would have a higher risk than individuals at the threshold for osteoporosis. In populations of osteoporotic individuals many patients would have a T-score of <-2.5 and the risk of vertebral fracture higher therefore than that at the threshold (Table VII).

As previously discussed, the parallel assessment of a number of risk factors with or without BMD assessment permits the identification of groups or individuals at high risk. It is of interest that the combination of relatively few risk factors can yield relative risks of five or more. The relationship between relative risk and 10-year probability of vertebral fracture is shown in Table VIII[17].

SINGAPORE IS NOT SWEDEN

Many of the estimates for fracture probabilities are derived from Sweden. The strength of the use of the data from Sweden is that accurate statistics are available on a national basis. There is, however, a concern with regard to applicability in different countries. The calculation for ten-year probabilities of fracture depends upon knowledge of fracture hazard and mortality hazard and there are differences between the two countries (Table IX). Life expectancy is slightly less and hip fracture incidence considerably lower in Singapore compared with Sweden[20]. Ten-year probabilities are lower in Singapore than in Sweden by a factor of 0.62.

Although poorly studied, the available information indicates that where risks of hip fracture are lower in one country by a given amount, so too are the risks of other osteoporotic fractures. Thus, the probabilities in Tables VI-VIII should be downward adjusted by a multiple of 0.62.

The level of risk that demands intervention or further assessment depends upon many factors including the risks and benefits of intervention. If for the sake of argument a probability in excess of 10% were unacceptable then women with a relative risk of two after the age of 65 years would fall within the treatment threshold and for men the age would be 75 years. In Singapore, the same probability is achieved at the same age with a population relative risk of 3.0 in men and women. In younger women at the age of 55 years the threshold is not exceeded in either country, except at very high relative risks (5.0 or more; see Table VIII). The setting of such thresholds will in part depend on

health economic considerations. Such studies will be important for optimising the selection of individuals for treatment and thereafter in the development of screening strategies.

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