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Diagnosis of Osteoporosis

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The incidence of many types of fracture increases logarithmically with age in both sexes and a great deal of evidence indicates that this is causally related to the changes in the amount of bone tissue present at these sites. The factors involved in the amount of bone present and hence the risk of fractures in adult life are peak bone mass attained in early adulthood and the amount of bone lost, for example, during the course of disease or after the menopause. The determinants of the peak bone mass and bone loss differ and both may be affected by diseases, environmental factors and by treatment. There are, however, few convincing data to suggest that peak bone mass can be influenced by therapeutic strategies [1,2], so that the determination of risk of individuals is more appropriately targeted in later life.

The loss of bone that occurs in osteoporosis is associated with several other structural and qualitative abnormalities that contribute to the loss of skeletal strength. These include changes in the turnover of bone and hence the rate of repair of fatigue damage, and the loss of connectivity of the trabecular elements which comprise cancellous bone. These and other abnormalities are collectively termed alterations in the quality of bone. Although these contribute to skeletal weakness, some of these changes in the quality of bone are the direct consequence of bone loss itself. Over and above this, bone mass is not the sole determinant of fracture risk. For any given bone mass, the risk of fracture is greater in the elderly, in part because of an increased tendency to fall and a decreased ability to react appropriately to diminish the force of impact. For these reasons the contribution of peak bone mass, skeletal and extraskeletal factors to hip fracture risk varies according to age [1,3].

Despite this multiplicity of factors, attention has focused on the measurement of bone mass rather than other determinants of fracture risk, largely because of the variety of non-invasive techniques that are now available for the measurement of bone mineral content or bone mineral density (BMD). Moreover, osteoporosis is currently defined in an operational sense from the measurement of BMD and these techniques have taken a pivotal place, not only in the diagnosis of osteoporosis but also as a prognostic measurement to assess the probability of future fractures [1].

Over the past several years a consensus definition of osteoporosis has emerged. It is defined as: 'A systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk' [4]. Although many factors other than BMD contribute to fracture risk these are not readily measured, and for this reason it is appropriate to consider practical definitions of osteoporosis in terms of the amount of bone present. Osteoporosis defined in this way is therefore the measurement of a risk factor – albeit an important factor – to provide a diagnostic or prognostic index of risk. This paper reviews the current strengths and limitations of this approach.

Definition of Osteoporosis

Because of the high accuracy of techniques to measure bone mass, these can be used as tests for osteoporosis, and within this general framework, several approaches have been used. One has been to consider osteoporotic patients as those in whom measurements fall below the range for the young healthy adult population [5,6] or lie within the lowest quartile, quintile or decile of the young healthy female reference range. Others have defined osteoporosis as a bone density below the age-adjusted reference range or 1 standard deviation (SD) below the mean for a particular age.

A second approach has been to characterize the osteoporotic population to derive a 'fracture threshold' based on a range of density measurements in the population with vertebral or hip fractures. This can be arbitrary, set for example at 2 SD above the mean value of patients with osteoporotic fracture [7,8].

A third approach, again based on densitometric measurements, is to utilize such values to derive a lifetime fracture risk [9,10].

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All approaches aim to stratify individuals within a reference range. The apparent prevalence and incidence of osteoporosis will depend upon the cut-off value chosen. The examples given above yield a 32-fold range in the apparent prevalence of osteoporosis [1]. Cut-off values should, therefore, be appropriate for the use of any diagnostic assessment which might be set at the level of BMD that is associated with an unacceptably high risk of fracture. Thus, the most straightforward approach for the diagnosis of osteoporosis is to define a 'fracture threshold', namely a cut-off for BMD which captures most patients with osteoporotic fractures.

The distribution of BMD in adults at skeletal maturity approximates a normal distribution. A cut-off value below 2.5 SD of the healthy young reference range for adult women is appropriate in most models, particularly for hip fracture [11]. More than one cut-off can be chosen to denote severity of disease. This permits four general diagnostic categories to be established for women of any age [12] (Fig. 1), and the following have been accepted by the European Foundation for Osteoporosis and Bone Disease, the National Osteoporosis Foundation of the United States and the World Health Organization [1]:

Normal: A value for BMD or bone mineral content (BMC) greater than 1 SD below the average value of a young adult.
Low bone mass (or osteopenia): A value for BMD or BMC more than 1 SD below the young adult average but not more than 2.5 SD below.
Osteoporosis: A value for BMD or BMC more than 2.5 SD below the young adult average value.
Severe osteoporosis (established osteoporosis): A value for BMD or BMC more than 2.5 SD below the young adult average and the presence of one or more fragility fractures.

The diagnostic categories above identify approximately 30% of postmenopausal women as having osteoporosis,

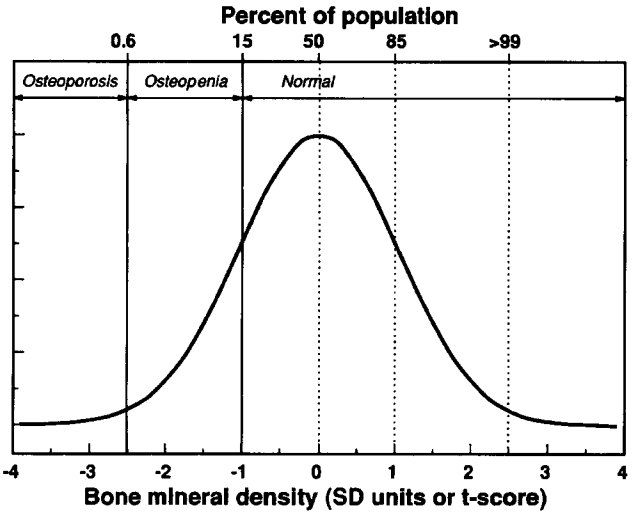

Fig. 1. Diagnostic thresholds for women based on the distribution of bone mineral density in the young healthy female population.

Table 1. Proportion (%) of white women with osteoporosis by age adjusted to 1990 US white women defined as a bone mass below 2.5 SD of the young adult reference range at the spine, hip or midradius

Age range (years)	Any site	Hip alone
30–39	0	0
40–49	0	0
50–59	14.8	3.9
60–69	21.6	8.0
70–79	38.5	24.5
80+	70.0	47.5
⩾50	30.3	16.2

utilizing measurements at the spine, hip and forearm (Table 1). The prevalence of osteoporosis is approximately equivalent to the lifetime risk of fracture at any of these sites. When measurements are made at one site alone, then the prevalence is 15–20%, comparable to the lifetime risk of a single osteoporotic fracture such as hip fracture. Because the distribution of values for BMD in the young healthy population is Gaussian, the incidence of osteoporosis increases exponentially after the age of 50 years, as is also the case for many osteoporosis-related fractures.

The diagnostic use of bone mineral mass measurements in this way has several general limitations as well as limitations specific to a particular methodology, which are important to recognize.

Limitations in Diagnosis

Since bone mineral mass or density is continuously distributed in the population and since the risk of fracture is also continuous, in the absence of fracture, there is no absolute criterion that can be made to delineate an individual with the disease from one without. In this sense, the concept of disease differs from that of, say, leukaemia where the individual either has or does not have the disease even though it may be variously clinically overt or covert. For this reason, there is an overlap between BMD of populations with and without fracture, irrespective of the technique used and the cut-off chosen and the site of measurement. Indeed, the risk of fracture is stochastic, increasing progressively as BMD decreases [1].

The reference ranges described are applicable to women, but different criteria should be applied in the case of men and in younger individuals before skeletal maturity. In men the risk of fracture is substantially lower for a bone mineral measurement within their own reference range so that a more stringent criterion is appropriate to yield the same risk as in women. The use of the same value of BMD as a cut-off as that used in men gives approximately the same absolute risk of vertebral and of hip fracture in preliminary studies and is a useful starting point.

Because of the multiplicity of techniques and the systematic differences in BMD measurements even at the same site with different equipment, standard deviation units are preferred. Recent attempts to standardize some sites may improve the complexity of using *T*-scores, but individuals will still be characterized differently according to the site measured and the technique, the equipment and the reference population used. The choice of a reference range is important for the accurate categorization of patients, as too is the estimate of variance. In many countries reference ranges are not available for young healthy adults, and the use of manufacturers' ranges may be misleading. Published ranges that appear to be appropriate for the United States and Northern Europe are not necessarily appropriate for other countries.

It is also important to recognize that individuals may be deemed osteoporotic at one skeletal site and not at another. For this reason terms such as spinal osteoporosis may be preferred. Moreover, the measurement of BMD at two or more sites will increase the apparent prevalence of osteoporosis. It has been suggested that the use of two sites would improve fracture prediction and there is evidence is to support this view, but the gain is small [13]. The poor predictive value of BMD measurements between sites inevitably means that errors of misclassification will occur frequently. Serious errors of classification are, however, relatively uncommon (Fig. 2).

The test becomes invalid in the presence of other disorders, particularly in the presence of osteomalacia. A low BMC can only be interpreted as measuring a low bone mass where the bone tissue itself is normally mineralized. Osteoarthrosis, vascular calcification, fracture and scoliosis also impair interpretation depending on the site chosen. Overlying metal objects and contrast media affect the result too. The problems of osteoarthrosis affect both the spine and hip, though much more so at the spine [14].

A major problem with the use of densitometry is the availability of instruments. The 'density' of dual-energy X-ray absorptiometry (DXA) varies remarkably around the world. Even within Western Europe there is a 15-fold range in availability. Very conservative estimates suggest that approximately 3–4 units/million is appropriate for the non-screening and diagnostic use of BMD, though higher numbers would be required to monitor treatment [15]. Until those targets are achieved, the diagnosis and treatment of osteoporosis are analogous to the diagnosis and treatment of hypertension without a sphygmomanometer.

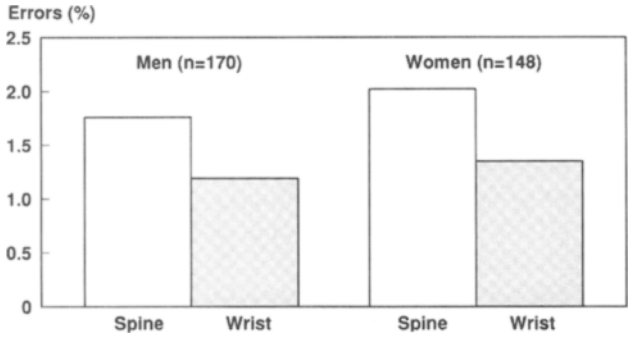

Fig. 2. Serious errors of classification in a random sample of elderly men and women. Individuals were characterized as normal, osteopenic or osteoporotic according to BMD measured at the hip. Classification errors indicate the proportion of individuals classified as osteoporotic at the hip but normal at the spine or wrist, *or* normal at the hip but osteoporotic at the spine or wrist.

Finally, it is important to recognize that diagnostic thresholds are not necessarily intervention thresholds. For example, the significance of osteopenia is quite different at the age of the menopause and at the age of 80 years. In the former, a case can be made for prevention of osteoporosis, whereas in the latter the lifetime risk of fracture is low.

Limitations of the Techniques

The diagnostic power of measurements of skeletal mass or mineral content depends upon various aspects of accuracy [1]. Accuracy can be defined as the ability to obtain a test result that is similar to the true value it was intended to measure. The 'true value' in terms of the diagnosis of osteoporosis has been variously defined as the amount of skeletal calcium at the site measured or at another site, or the presence or absence of fracture at other sites. Different techniques incur different errors of accuracy.

None of the techniques utilized give measurements of true bone density. For example, both single photon absorptiometry (SPA) and DXA provide information on bone mineral content (BMC, g). BMC is assessed from a single projection, most commonly an antero-posterior projection, so that the content can be adjusted, for example, to the area of the vertebral bodies visualized to give an estimate of apparent areal density (BMD, g/cm^2). Other adjustments include muscle mass and the width of bone. It is important to recognize that none of these adjustments provides measurements of the true density of bone and each adjustment incurs errors. For example, at the spine a BMC of, say, 15 g measured in two individuals, one with a vertebral area of 12 cm^2 and the other of 15 cm^2, would give an apparent 'density' of 1.25 g/cm^2 and 1.00 g/cm^2 respectively – a difference of 20% between the latter and the former. Assuming the vertebra is cylindrical and the difference between patients is in vertebral width, the true mineral densities would be 0.456 g/cm^3 and 0.31 g/cm^3 – a difference of 30% [16]. The adjustments also have effects on the variance of measurements observed in the population, the differences between sexes, and may affect their ability to discriminate individuals with and without osteoporosis [17]. A number of adjustments have been proposed to correct for areal density (for example by measuring vertebral dimensions on lateral views of the lumbar spine) and appear to improve prediction of fracture risk at the spine [18].

Comparisons of Sites

Invasive techniques such as ash weight or histomorphometry at various sites have shown variable relationships between sites. For example, the correlation between cancellous bone volume at the ilium and lumbar spine is reported as 0.83 despite a 2-fold difference in the mean value [19]. Similarly, the ash weight of the metacarpals correlates closely with ash weight of the mid-radius (0.96) or femur (0.85) [20]. In contrast, the correlation between metacarpal ash weight and vertebral ash weight is poor ($r = 0.47$). Thus, measurement at a cortical site is less likely to predict ash weight at another cancellous bone site, but more likely to predict ash weight at another cortical site.

Although the correlations are statistically significant, they are not sufficiently close for the prediction of one parameter from the other. For example, measurements at the forearm cannot be used to predict BMC at the spine [21].

Thus, to diagnose vertebral osteoporosis, measurements at the spine are appropriate, whereas other sites are more appropriate in other circumstances. Within the limitations of accuracy discussed later, a diagnosis of generalized osteoporosis can be made from any site.

Given the choice of a site, measurements made by different techniques give similar results [1]. For example, both SPA and DXA perform similarly in vivo in assessing the calcium content at the forearm. There are close correlations in the order of 0.8–0.9 between vertebral densities assessed by quantitative computed tomography (QCT), DXA or dual photon absorptiometry (DPA), and even higher comparing DXA and QCT ex vivo ($r = 0.96$).

Comparative Accuracy

All techniques incur some errors of accuracy. Systematic inaccuracies occur particularly at the spine since the vertebrae are irregular in shape and apparent density and mineral content will depend in part upon the algorithm utilized for edge detection. Different machines give different results even at the same site and with similar technology. For example, values for BMD at the lumbar spine using the Hologic DXA give values 0.1 – 0.14 g/cm^2 lower than values using the Lunar machine. This difference (approximately 10%) is roughly equivalent to a standard deviation of the population range of BMD. Notwithstanding, there are close correlations between the two methods at the spine [22]. It is more problematic at the hip since the slope between the measurements is not equal to unity [23].

Systematic errors also alter the apparent normal range for bone density in the population, and at the spine of the variance of populations measured by DXA may differ by as much as 20%. A change in the apparent population variance may change the ability to position an individual accurately within a population range.

These factors have some impact on diagnostic accuracy but the greatest concern is the presence of non-systematic errors of accuracy. The lower the accuracy, the less confidently will ash weight be predicted from BMD. There is a great deal of evidence to suggest that all the techniques used for diagnosis incur this type of error. Major sources of error include osteoarthrosis at the spine and the heterogeneous disposition of soft tissue surrounding bone.

Variable soft tissue densities are a particular problem at the spine. The vertebrae are surrounded by a thick layer of lean body mass, fat mass and air, the composition of which varies widely from one person to another. BMC is underestimated in obese subjects unless adequate fat correction is performed. The correction for fat makes a number of assumptions [24] that are difficult to assess. The most important is to assume homogeneous disposition of fat in the body, so that non-systematic errors arise because of the variable fat content of the kidney capsule [25]. Fat composition also varies within individuals and, for example, the menopause is associated with an increase in fat content of surrounding tissue as well as that within cancellous bone [26]. Conversely, some treatments decrease the proportion of fat in soft tissues without necessarily affecting body weight. These effects complicate the assessment of changes in bone density induced by exercise, oestrogens, the anabolic steroids and in corticosteroid-induced osteoporosis [2]. The errors are greater with QCT at the spine and less with absorptiometry at the forearm.

Many investigations have reported the accuracy of various techniques. The vast majority have assessed accuracy in vitro, for example on phantoms or on excised skeletal tissue. As might be expected higher estimates of accuracy are generally derived in such circumstances than from studies on cadavers. The estimate of accuracy most relevant to diagnosis is that derived as closely as possible from the situation in vivo, particularly for sites with a large soft tissue component. These range from 2% to 10% [1].

The accuracy of the various techniques has to be considered alongside the variance in measurements of the population to be examined, which ranges from 10% to 50%, depending upon the techniques used for measurement and any normalization procedures applied [27,28]. In general, the variance (CV%) is no greater than 20%. It is evident, therefore, that techniques with an accuracy error in the order of 10% cannot be used to define osteoporosis where the population variance is in the order of 20% or less. Of the techniques widely available, the accuracy performance in relation to the population variance is highest in the case of SPA by a factor of 2-fold or so [28]. This might suggest that SPA should be the technique of choice for diagnosis utilizing the single estimate of bone density, but an appendicular measurement (at the wrist) is approximately two-fold weaker than DXA at predicting bone mass at the spine or hip, so that there is little to choose between them.

Sensitivity and Specificity

Many studies have examined the sensitivity and specificity of bone mass measurements to discriminate osteoporotic patients with fracture from populations without fracture [6,7,29]. In general, both sensitivity and specificity are improved by measuring sites of biological relevance. Thus, measurements of vertebral BMC have a higher predictive value for the detection of spinal fractures than measurements at the wrist. Conversely, greater predictability is obtained for the detection of wrist fractures by measurements at this site than by measurements at the spine [30], but this is not an invariable finding [31,32]. This does not necessarily influence the site to be chosen since the diagnosis of fracture is clinically obvious with a predictive value much greater than can be obtained with density measurements. The strength of such measurements in this context is only in the ability to provide information on whether the fracture is associated with a reduced bone density.

Bone Mineral Density as a Prognostic Tool

Accuracy when defined as the degree to which BMD can measure the amount of bone mineral at any particular site is important in establishing the diagnosis of osteoporosis. In the context of a prognostic measurement, the accuracy of BMD is the ability of bone mineral measurements at any one site to predict the probability of osteoporotic fracture at that site or elsewhere in the future [1]. This application is of crucial importance in developing treatment and preventive strategies.

The practical value of the assessment of BMD in this context depends on the gradient of risk associated with a reduction in BMD. The greater the increase in risk for a finite reduction in BMD the more useful the test, since more individuals will be identified correctly to be at either high or low risk. A large number of studies principally in women have examined fracture risk in cohorts of varying ages for up to 20 years [1]. Estimates consistently show a risk gradient of between 1.5 and 3 for each standard deviation decrease in BMD with all the absorptiometric techniques. The performance characteristics of bone mineral measurements is somewhat greater than those reported for serum cholesterol or hypertension and the risk of coronary artery disease in men (Fig. 3).

As recognized many years ago, the traditional concepts of sensitivity and specificity collapse when continuous variables are considered [33]. A useful analogy to illustrate this point is provided by the relationship between blood pressure and stroke. At any point in time most hypertensive patients do not have strokes, which means that high blood pressure has low specificity for the diagnosis of stroke. This should not be taken to mean that high blood pressure does not increase the risk of strokes: the correct interpretation is that high blood pressure is common in those who do not have strokes. In other words the apparent specificity of high

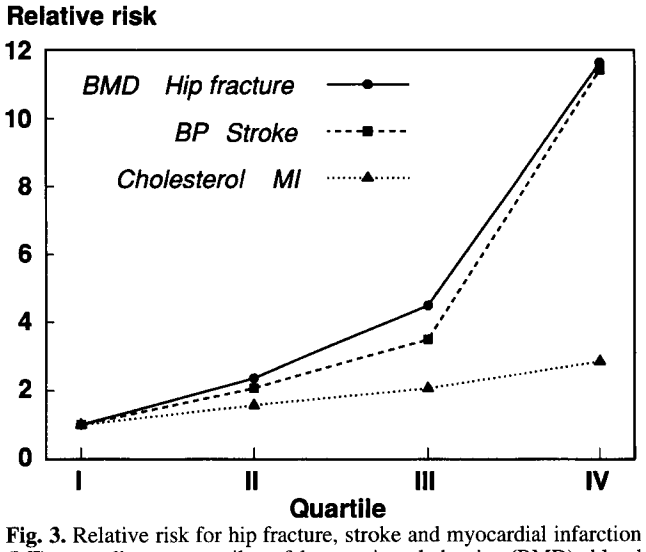

Fig. 3. Relative risk for hip fracture, stroke and myocardial infarction (MI) according to quartiles of bone mineral density (BMD), blood pressure (BP) or serum cholesterol.

blood pressure or low BMD is only a measure of the prevalence of those risk factors in the community. This does not, however, invalidate the use of blood pressure measurements to identify individuals at risk from stroke, nor of BMD measurements to predict fracture.

In the context of osteoporosis (and hypertension) the lifetime risk rather than the presence or absence of a fracture is the appropriate referent. In this way sensitivity is defined as the proportion of individuals who would in their lifetime sustain a fracture with a BMD below a defined cut-off value. Specificity is defined as the proportion of subjects who would not sustain a fracture in their lifetime with BMD values above a given cut-off value for bone mineral.

Table 2 provides some estimates of sensitivity and specificity under a number of different conditions [1]. The gradient of risk of hip fracture for each standard deviation drift in BMD is modelled at 1.5, 2.0 or 2.5 – which conservatively covers the range identified in prospective studies. The average lifetime risk of hip fracture is modelled at 15%, which is also a conservative estimate for women from the USA and Northern Europe.

The sensitivity and specificity of an assessment of BMD to predict fracture depend critically upon the cut-off point used to define a high-risk category. The more stringent the criteria the greater the specificity and the lower the sensitivity. In the table, two cut-off values for BMD are given, namely the lowest 6.5% or the lowest 30% of the perimenopausal population, which corresponds to the range over which intervention might be contemplated. Considered in this way the false-positive rate is close to zero, indicating that the specificity of bone mineral measurements is high since the lifetime risk of fracture is close to 100% using the 6.5% cut-off. When a 30% cut-off is used the specificity remains high (over 75%) over all ranges of risk assumption. In contrast, the test lacks sensitivity (38–81% depending on the assumptions made). The relatively low sensitivity

Table 2. Prediction of hip fracture assuming a lifetime risk of 15% in women according to gradient of risk and cut-off values for bone mineral density [1]

	High risk-category					
	6.5%			30%		
Gradient of risk	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
1.5	38	98	89	65	75	74
2.0	47	100	92	75	77	77
2.5	52	100	93	81	77	78

indicates that a substantial proportion of fractures will occur in women who lie in the lower risk groups when BMD is used as a single test to assess fracture risk. The low sensitivity of BMD assessments is one of the reasons why this technique alone cannot be used for population screening.

Optimization of Risk Assessment

From Table 2 it is clear that sensitivity increases as the gradient of risk of fracture with the mineral measurement increases. This indicates that improved accuracy would increase the sensitivity of the test. There are a number of ways in which this might be achieved, either by the optimization of density measurements or by using additional indices of risk [34].

Site-Specific Measurements

Measurement at a specific site vulnerable to fracture improves the accuracy with which to predict fracture at that particular site. In other words, accuracy is improved by site-specific measurements. In one study, assessment of BMD at the mid-radius or distal radius or lumbar spine was associated with an approximately 1.5-fold increase in risk of hip fracture for each standard deviation decrease in BMD. In contrast, measurements at the hip gave gradients of risk between 2.5 and 3.0 [35]. Thus site-specific measurements, although they do not improve the prediction for all fractures, do improve the prediction for fractures at that particular site.

An important caveat is that most prospective studies have been of relatively short duration (less than 10 years). The accuracy of bone mineral assessments to predict hip fracture 20–30 years thereafter is likely to be less. Since the average age of hip fracture is 80 years or more in Western Europe, screening strategies for hip fracture based on BMD are likely to be most beneficial when directed at women 10 or 20 years after the menopause.

Combined Assessments

Bone mineral assessments at one site correlate imperfectly with measurements at other sites. It has been suggested that the measurement of bone mineral at multiple sites would improve the prognostic value of densitometry. Provided that site-specific measurements are made, there appears to be little value in assessment at other sites [36]. On the other hand, techniques that capture elements of bone strength in addition to density or mineral content may have added value. In a recent study the use of ultrasound at the heel was shown to have a prognostic value for hip fracture risk independently of bone mineral measurements at the femoral neck [37].

Indices of Skeletal Losses

BMD at any given postmenopausal age is a function of peak bone mass and the amount of bone lost. Thus, with age in men and women, but particularly in women, bone mass will be determined increasingly by the amount of bone lost after the age of 50 years. Though variable at different skeletal sites, the contribution of peak bone mass and bone loss to skeletal deficit is approximately equal at the age of 65 years [2]. There has been a great deal of interest in the use of biochemical indices of bone turnover to assess rates of bone loss in postmenopausal women. Analytes shown to be of value include serum activity of alkaline phosphatase, particularly the bone derived fraction, serum osteocalcin, the fasting calcium/creatinine ratio, urinary excretion of hydroxyproline, pyridinoline crosslinks and some of their associated peptides.

Clinical evidence indicates that rates of loss can be predicted from a panel of biochemical estimates in the early postmenopausal years [38–41]. Long-term prospective studies over a 15–year period indicate that high rates of bone remodelling are associated with an approximately 2-fold increase in fracture rates [42]. In this cohort of perimenopausal women peak bone mass of fast and slow losers were identical, suggesting an independent contribution of bone loss measured in this way to fracture risk. Prospective studies are required to determine whether such measurements would improve

specifically the identification of those at risk from hip fracture, but the persistence of high rates of bone remodelling and indeed acceleration in the very elderly [43,44] suggests that this may be so. It seems likely that indices of resorption (rather than resorption and formation) will provide prognostic value in elderly women. In a recent prospective study, resorption rates as judged by the assay of type I collagen C-telopeptide were significantly higher among hip fracture cases than amongst controls, but there were no significant differences in the biochemical indices of bone formation [45]. High rates of resorption were associated with a 2-fold higher risk of hip fracture.

The Shape of Bone

The geometry of bone appears also to be an important factor in hip fracture risk. For example, the risk of hip fracture increases in women with the length of the femoral neck [46]. After adjustment for age, each standard deviation increase in hip axis length appeared to double the risk of hip fracture (odds ratio = 1.8; 95% CI 1.3–2.5), an effect more marked at the femoral neck (OR = 1.9; 95% CI 1.3–3.0) than at the trochanter (1.6; 95% CI 1.0–2.4). The effect is independent of bone density and may explain some of the density-independent differences in risk between countries [47].

Extraskeletal Risk Factors

Density-independent components of fracture risk such as falls are clearly important for hip fracture. For any given bone denisty, the risk of hip fracture is greater in the elderly. The increased frequency of falling, the type of fall that occurs in the elderly and the loss of protective soft tissue covering may all account for the larger contribution of 'age' and relatively smaller contribution of bone mass which is seen in later life [3]. A variety of simple tests have been devised to assess postural stability and have been shown to be associated with increased risk of hip fracture independent of BMD [48].

Prior Fractures

The risk of fracture is substantially increased in the presence of a prior fragility fracture [13,49]. In the case of hip fracture the risk is approximately doubled, even adjusting for BMD [50].

Other Risk Factors

A very large number of clinical risk factors have been identified, largely from epidemiological studies. In some cases they may be imperfect surrogates for bone mass or for the risk of falling. In many cases their causal relationship to hip fracture risk is conjectural but this does not negate their potential value in the identification of individuals at risk.

Towards a Strategy

The operational definition of osteoporosis is based on the assessment of BMD and is therefore the corner-stone for risk assessment. The multiple factors outlined above that contribute to risk more or less independently of bone mass suggest that the gradient of risk between those characterized as being at high or low risk can be markedly increased by assessments that contribute to risk independently of BMD [34].

The aim of evaluation of fracture risk is primarily to target interventions to those at highest risk. In this context lifetime risk rather than relative risk is the more appropriate measurement. For example, a 3-fold increase in risk for hip fracture has greater significance in an individual at the age of 50 years with a normal life expectancy than in a 100-year-old with a 6-fold increase in risk. The relation between average lifetime risk with age can be used to assess the risk associated with the presence or absence of risk factors [51]. The presence of osteoporosis at the hip (a BMD measurement 2.5 SD or more below the average of the young healthy female population) is expected to increase the relative risk of hip fracture at least 4-fold in the 50-year-old woman. Thus, in osteoporotic women at the age of 50 years the lifetime risk of hip fracture is approximately 50% and for any osteoporotic fracture close to 100% (Fig. 4). Up to the age of 70 years the lifetime risk of hip fracture is relatively constant for a given BMD at least until the age of 70 years. This suggests that all women below the age of 70 years with osteoporosis should be offered treatment, but also indicates that many with osteopoenia have an unacceptably high risk.

The use of density-independent components in risk assessment can be used to enchance the population deemed to be at unacceptable risk. An obvious example in the elderly is the presence of a prior fragility fracture,

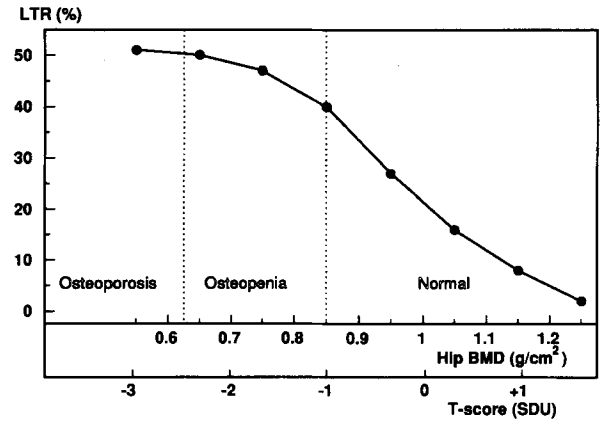

Fig. 4. Average lifetime risk (LTR) for hip fracture in women at the age of 50 years as a function of bone mineral density (BMD) at the hip.

which increases the risk of further fractures by at least 50% irrespective of bone density. Thus, the presence of a prior fragility fracture in a woman up to the age of 70 years would carry a 2-fold increase in lifetime risk of hip fracture with a BMD value substantially less than a *T*-score of 2.5. Similarly, a 70-year-old with a prior fragility fracture, a high rate of bone resorption, a long hip axis and postural instability would have a 100% risk of hip fracture with a bone density *T*-score of 1.5, though few osteopenic individuals would have this combination of risks.

For these reasons the use of risk assessments in addition to bone mass enhances considerably the prognostic value of density measurements and enlarges the population that can be confidently treated. The cut-off point for lifetime risk of fracture that is unacceptably high is not determined and depends largely on health economic considerations. In this context screening of the elderly shortly before hip fracture is common (say at 65 years) may provide distinct advantages over screening perimenopausal women. Not only are some of the risk factors (prior fracture, postural instability) more common at a later age, but the ability of all assessments to predict hip rather than other fragility fracture is more secure. Finally, treatments of finite duration are most cost-effectively targeted in the elderly [1]. Thus, enhanced risk prediction of fracture will help define not only treatment strategies and intervention thresholds, but also the risks and benefits of different screening policies.

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