
A New, Standardized Approach to Fracture Risk Interpretation

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Screening for osteoporosis has been hampered by the absence of a standard approach to the interpretation of bone density and other risk factors. A consensus conference of international experts has now recommended a report which is based upon two concepts: (1) comparison of an individual's bone density to the mean value for 30 year old women, and (2) estimation of Remaining Lifetime Fracture Probability (RLFP), based upon current age and bone density, life expectancy, future bone loss, and other risk factors. This model is dynamic and can be perfected as new risk factors become established. It also allows for estimation of therapeutic impact, and thus improves and individualizes clinical decision making.

Despite the substantial body of evidence linking bone density to future fracture risk, few successful osteoporosis screening programs have been implemented. This can be attributed to two obstacles:

1. The dearth of treatment options
2. The absence of a standardized interpretation of bone density and fracture risk

With the availability of the bisphosphonate class of drugs, and the future potential of estrogen analogues, the first obstacle has been overcome. However, the second obstacle remains. A woman having spinal bone density measured in Honolulu might receive an entirely different report and interpretation if her hip bone density were measured in New York. There has been no consensus regarding which levels of bone density should be considered "treatment thresholds."

To address this important issue, a Consensus Conference of international experts convened in Chantilly, Virginia in April, 1994.¹ In order to understand the conclusions of the consensus panel, some background is helpful.

Bone mass (or density) is clinically useful for one reason; it is a strong risk factor for osteoporotic fractures. It could also be argued that bone density measurements are clinically useless unless they influence the management of individual patients. The greatest, potential application of bone density is in patients *without* fractures, but who are *at risk* for fractures. Since such patients have no symptoms, and since there are usually no signs or other risk factors that can successfully identify individual patients who are at risk, there is a great clinical need for a practical way in which to identify such patients. Otherwise pharmacologic agents, including estrogen and especially anti-resorptive drugs, cannot be selectively prescribed for those with the greatest need.

If bone density measurements are to successfully fulfill this need, then they must indicate to the physician how to manage the individual patient. If the patient is a 50-year-old woman, for example, the question to be answered is: Should this patient receive pharmacologic agents, or is only life-style advice required?

Bone density is the only known risk factor which has the potential to answer this question. However a report stating that a patient has a *normal* spine BMD of 1.0 gm/cm² does not answer the referring physician's question. Thus there is a need to develop a consensus on how to provide a *useful, clinical* interpretation of bone mass measurements.

Etiologic Risk Factors Versus Clinical Risk Indicators

In order to understand the clinical use of bone density, it is helpful to discuss risk factors in general. Risk factors have two possible uses:

1. To search for disease etiology.
2. To clinically identify individuals at greatest risk of disease.

An example of an etiologic risk factor is smoking (for lung cancer). In addition to explaining etiology, there are obvious public health implications. On the other hand, smoking does not *diagnose* lung cancer, even though it may raise the clinical suspicion.

There are some risk factors that are sufficiently strong that they might be termed *clinical risk indicators*.¹ The relationship of blood pressure to cardiovascular and stroke risk is sufficiently strong that the blood pressure measurement itself becomes an indication for treatment. However, hypertension is not the only risk factor for stroke. Likewise, bone mass is not the only risk factor for fracture.

The problem is this: How can these fracture risk data be applied to clinical practice? It is certainly not intuitively apparent to the clinician what a lumbar spine bone density of 1.0 gm/cm² means for a 50-year-old patient. A variety of different interpretations have been employed in the past. Before discussing each of these, the consensus panel first discussed the requirements that an interpretation should fulfill:

1. It should convey the fact that peak bone mass is as relevant as is bone loss in determining lifetime fracture risk.

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| Initial BMD | Initial Age | RLFP (untreated) | 90% Reduction in Loss Rate | |
|-------------|-------------|------------------|----------------------------|-------|
| | | | NFP | CFP |
| 510 | 50 | 0.46 | 0.38 | 17700 |
| | 80 | 0.07 | 0.03 | 62050 |
| 360 | 50 | 2.50 | 1.98 | 3400 |
| | 80 | 0.49 | 0.19 | 9650 |
| 290 | 50 | 5.00 | 3.75 | 1800 |
| | 80 | 1.11 | 0.39 | 4500 |

2. It should illustrate how the individual compares to healthy, young individuals of the same sex. For this purpose, the mean bone density of healthy, 30-year-old women is considered the standard of reference.

3. It should be intuitively apparent to both physician and patient.
 4. It should provide an indication of absolute fracture risk.
 5. It should estimate cumulative fracture risk over the patient's (estimated) remaining lifetime.

6. It should give the physician an objective basis upon which to make therapeutic decisions. It should address this question: "Will this patient benefit from pharmacologic treatment?"

7. It should also provide an estimate of therapeutic impact upon fracture probability.

8. It should be adaptable to include risk factors other than bone mass.

9. It should be sufficiently generic that various measurement techniques and sites can be employed.

10. Since there are data indicating that density measurements at various skeletal sites may contain independent predictive value for fractures, our interpretation should be able to incorporate all available information. Thus if two bone density measurements are available, both should be used, rather than arbitrarily discarding one value in favor of another.

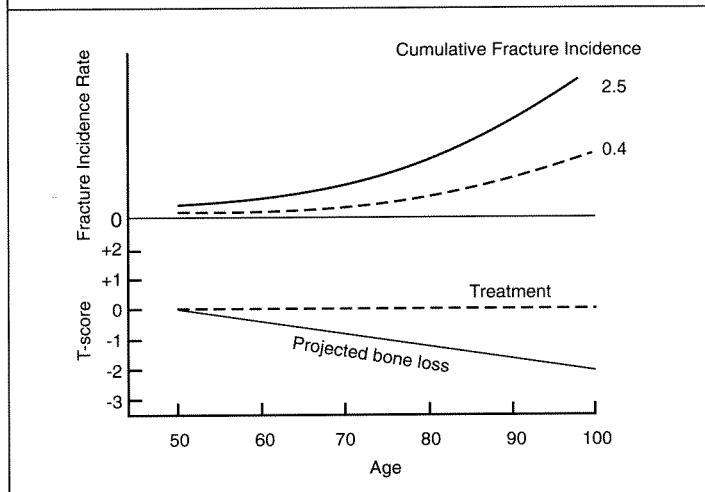
Based upon these criteria, the consensus panel agreed upon the following approach to fracture risk interpretation (Fig 1).

Based upon prior recommendations of the World Health Organization, bone density values between -1.0 and -2.5SD are considered osteopenic, and bone density values more than -2.5SD are osteoporotic. If the patient also has a history of nonviolent fracture, she is classified as having *severe osteoporosis*. Although these classifications provide a useful cross-sectional description, they are insufficient for clinical decision making because they ignore age (and therefore future years of bone loss and risk exposure).

Therefore the consensus panel adopted the concept of Remaining Lifetime Fracture Probability (RLFP). Although the mathematical modeling involved is complex, the concept is simple, as illustrated in Fig 2. For purposes of discussion, assume that we are evaluating a 50-year-old female, (Pt. "A" in Fig. 2). Her current bone density is 0.95 SD below the mean for 30-year-olds; thus she has a *T-score* of -0.95. Based upon life tables, we estimate that her life expectancy is an additional 32 years. We will assume that, on average, she will lose bone density at the rate of 1.5% per year over 32 years; if serial bone density measurements are available, this figure can be appropriately adjusted for the individual.

Based upon data from published studies relating fracture rates to levels of bone mass/density, a fracture incidence rate can be assigned to each age and bone density value. For example, our 50-year-old patient with an initial heel value of 360 mg/cm² has a 0.5% probability of a fracture (at any skeletal site) during the next year.

Fig 1.—Each age and BMD level is associated with a fracture incidence rate; the cumulative total of these rates represents cumulative fracture incidence (Remaining Lifetime Fracture Probability).



Each subsequent year, this rate increases as bone density declines. RLFP is nothing more than the sum of all these rates over an estimated remaining lifetime of 32 years. Thus this patient has an estimated RLFP of 2.7, meaning that, on average, women like her will experience 2.7 fractures in their remaining lifetime. This number is, of course, associated with an error; some such individuals will have more, and some will have fewer, fractures. Figure 2 also illustrates why bone density alone is not sufficient to make clinical decisions. Patient B, who is 75 years old, has a *T-score* very similar to Patient A, at -1.1. According to WHO guidelines, she is *osteopenic*, whereas Patient A is *normal*. However Patient B has an RLFP of only 0.5 (because of her shorter life expectancy), and a treatment that stops bone loss would only lower her RLFP to 0.3. Patient A, on the other hand, has an RLFP of 2.7, which could be substantially lowered to 0.3 with treatment. Thus the "normal" patient will receive much more benefit from pharmacologic treatment than will the older, "osteopenic" patient.

Although many fracture risk factors appear to be mediated via bone mass, not all fracture risk factors are expressed, or mediated, via bone mass. Falls, previous fractures, and perhaps age are independently associated with fracture risk. Nevertheless, bone mass is the most *clinically* useful of these indicators, for several reasons. Although falls in the elderly have shown an association with fracture, independent of bone mass, most fractures still occur in patients with low bone mass. Also, the decision to preserve bone mass should occur at much earlier ages, when the tendency to fall is not yet apparent. Finally, preservation of bone mass is likely to prevent many fractures even if falls cannot be completely eliminated. Age has also been associated with fracture risk, but of course age itself is not modifiable. In any case, age is probably serving as a surrogate for some other age-related factor.

Bone density is clinically useful because it represents a composite and cumulative index of many other risk factors, both past and present, including both genetic and life-style influences. Bone mass frequently is a measurable expression of unknown, or unmeasurable, risk factors. For example, adolescent nutrition and physical activity may exert a strong influence upon attainment of peak bone mass, but it may be difficult, or impossible, to retrospectively estimate in a 50-year-old patient.

It is not the purpose of this paper to review the data relating bone mass to fracture risk. A number of studies have now shown that

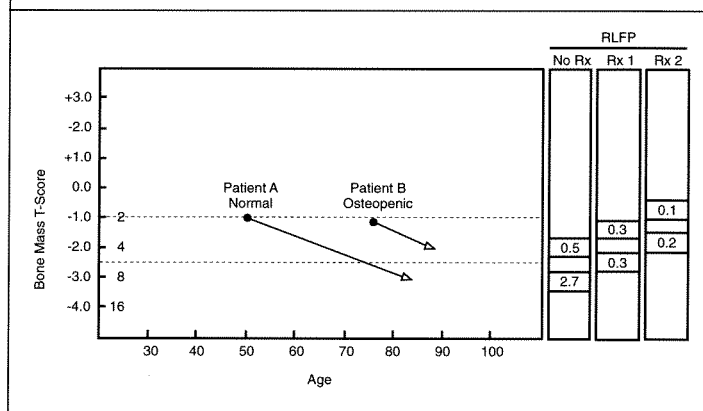
fracture risk increases progressively, and approximately exponentially, with decreasing levels of bone mass or density.³⁻⁵ Thus women with bone mass equal to the mean, one standard deviation (SD) below the mean, and two SDs below the mean, have two, four, and eight times greater risk, as compared to women with bone mass one SD above the mean.

RLFP thus addresses the need for a *cumulative* estimate of *absolute* fracture risk. It can also be applied to any bone density measurement for which fracture incidence data are available. However, the real advantage of the RLFP concept is the ability to estimate the impact of therapeutic intervention. Although knowing that this patient might experience fractures is more useful than knowing that her BMD is *normal*, it still does not tell the clinician what he or she most needs to know. Namely, can this risk be significantly lowered if pharmacologic treatment is prescribed? For example, if an anti-resorptive drug is prescribed, what is the impact upon fracture probability?

For the 50-year-old, an hypothetical, anti-resorptive drug that stops bone loss would reduce her RLFP from 2.7 to 0.3 (potentially preventing two fractures). However the 75-year-old, even if she achieves the same prevention of bone loss, only reduces her RLFP from 0.5 to 0.3 (preventing only 0.2 fractures). Because she has fewer years of future bone loss and risk exposure, there is less opportunity to reduce bone loss and fracture risk. Therefore, the older women may receive greater benefit from non-pharmacologic measures, such as calcium and Vitamin D supplementation, physical activity regimens, and possibly measures to reduce the risk of falls. The new treatments now becoming available are considerably more efficacious. The average patient might gain 8-10% bone density in the first three years of treatment, which translates into a 50% reduction in fracture risk. Thus treatment of older patients, like the 75 year-old mentioned above, becomes cost-effective, particularly if the treatment has a good safety profile.

A final, potential use of the RLFP model is to estimate cost-effectiveness of various treatment programs, shown in Table 1. If the cost of estrogen replacement is \$225 per year, and treatment continues indefinitely, *the cost per fracture-prevented* can be estimated. Surprisingly, these estimates suggest that pharmacologic treatments to reduce bone loss may be cost-effective even for women in their 70's, particularly for those at high fracture risk. Also new treatments that are either more potent, or which have a longer duration of action, could substantially improve the cost-effectiveness of treating the older woman. Although the reported bone mass increases from anti-resorptive agents typically plateau after 2-3 years of treatment, women who maintain such an increase might

Fig 2.—Standardized approach to bone density and fracture risk interpretation recommended by the Consensus Panel (1). Two patients with similar bone density, but different fracture probabilities. The y-axis compares the measured value to the average for 30 year old women. The arrow extends to mean life expectancy, and shows expected future bone loss. The younger patient has more future bone loss and risk exposure than the older patient, and may therefore receive greater therapeutic benefit. Treatment 1 assumes complete prevention of bone loss. Treatment 2 assumes a 10% increase in bone density.



have a much greater therapeutic benefit. For example, if the 50-year-old woman described above, with an initial bone density of 360 mg/cm² and an RLFP of 2.7, experiences a 8% gain in bone density which is subsequently maintained, it could translate into a new RLFP of 0.2.

In conclusion, a standardized approach to bone density and fracture risk interpretation is now available. Its use is expected to facilitate improved clinical decision-making, and to allow for individualized decisions for each patient.

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