Osteoporotic fracture risk assessment

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INTRODUCTION — Osteoporosis is a common disease that is characterized by low bone mass with microarchitectural disruption and skeletal fragility, resulting in an increased risk of fracture, particularly at the spine, hip, wrist, humerus, and pelvis [1]. Osteoporotic fractures (fragility fractures, low-trauma fractures) are those occurring from a fall from a standing height or less, without major trauma such as a motor vehicle accident. There were an estimated nine million osteoporotic fractures worldwide in 2000, of which 1.6 million were hip, 1.7 million forearm, and 1.4 million clinical vertebral fractures [2]. Fractures of the hip and spine are associated with an increased mortality rate of 10 to 20 percent [1,3]. Fractures may result in limitation of ambulation, depression, loss of independence, and chronic pain [4,5].

Properties that contribute to bone strength include bone mineral density (BMD), bone geometry (size and shape of bone), degree of mineralization, microarchitecture, and bone turnover [6]. BMD measurements are available to many patients, and fracture risk has been demonstrated to increase with decreasing BMD [6]. Assessment of bone microarchitecture requires methodologies such as high resolution peripheral quantitative computed tomography (QCT), high resolution or micro magnetic resonance imaging (MRI), or double tetracycline-labeled transiliac bone biopsy with histomorphometry, which are not routinely used in clinical practice.

Non-BMD factors that contribute to fracture risk include advancing age, previous fracture, falls, glucocorticoid therapy, family history of hip fracture and current smoking (table 1) [7-10]. Incorporating risk factors that are independent of BMD increases the sensitivity of fracture risk assessment and thereby improves treatment intervention strategies [11]. Univariate and multivariate analyses suggest that age, prior fracture history, and BMD are the strongest predictors of fracture risk [12].

Risk assessment for osteoporotic fracture will be reviewed here. Detailed information regarding screening, prevention, diagnosis, and treatment is found elsewhere. (See "Screening for osteoporosis" and "Prevention of osteoporosis" and "Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women" and "Clinical manifestations, diagnosis, and evaluation of osteoporosis in men" and "Overview of the management of osteoporosis in postmenopausal women" and "Treatment of osteoporosis in men".)

ASSESSMENT OF FRACTURE RISK — Low bone mineral density (BMD) is associated with increased risk of fracture. However, methodologies for combining BMD with clinical risk factors to quantify fracture probability offer attractive alternatives to relying on BMD testing alone [13]. Thus, assessment of fracture risk should include evaluation of both:

- BMD
- Clinical risk factors

Fracture risk should be expressed as absolute, rather than relative, risk. Absolute risk provides a better assessment of the probability of fracture and is more useful clinically for identifying patients most likely to benefit from therapy. The use of a fracture risk prediction tool is helpful in identifying the probability of fracture over a specified period of time, typically 10 years. (See 'Expression of fracture risk' below and 'Fracture risk assessment tool' below.)

Bone mineral density — In 1994, the World Health Organization (WHO) established a classification of BMD according to the standard deviation (SD) difference between a patient's BMD and that of a young-adult reference population. This value is now commonly expressed as a "T-score." A T-score that is equal to or less than -2.5 is consistent with a diagnosis of osteoporosis, a T-score between -1.0 and -2.5 is classified as low bone mass (osteopenia), and a T-score of -1.0 or higher is normal [14]. (See 'Dual-energy x-ray absorptiometry (DXA)' below.)

Many studies have demonstrated that low BMD is associated with an increased risk of fracture [12,15-21]. Individuals with T-scores of ≤-2.5 have the highest risk of fracture. However, because there are more individuals with osteopenia than

osteoporosis, the absolute number of fractures in subjects with T-scores in the osteopenia range is greater than in those with T-scores in the osteoporosis range [7-9,22]. Since most fractures occur in patients with T-scores better than -2.5, treatment strategies relying solely on BMD testing will miss many patients at risk for fracture who might benefit from interventions to reduce fracture risk.

Clinical risk factors — Assessment of clinical risk factors that are independent of BMD is important for fracture prediction. In addition to BMD, advancing age, prior history of fragility fracture, chronic glucocorticoid use, low body mass index (BMI), parental history of hip fracture, cigarette smoking, and excess alcohol intake are the risk factors that have been demonstrated to be most predictive of fracture (table 1). (See 'Clinical risk factor assessment' below.)

Clinical risk factor assessment alone may be considered for fracture prediction in world regions without access to any BMD measurement technologies [13,23]. The WHO Fracture Risk Assessment Tool (FRAX website) model allows estimation of 10-year probability of hip fracture and major osteoporotic fracture with clinical risk factors alone when BMD is not known [24-26]. (See 'Fracture risk assessment tool' below.)

Expression of fracture risk — Absolute risk (AR) is the probability of fracture, usually expressed as a percentage, over a specified period of time. Relative risk (RR) is the ratio of absolute risks of two populations [21]. RR tends to overestimate fracture risk in some populations and underestimate it in others [27]. As an example, a 50-year-old woman and an 80-year-old with a hip T-score of -2.5 each have the same RR for hip fracture compared to an age-matched population with normal BMD [21], while the 10-year probability of hip fracture is much higher in the 80-year-old (table 2) [28]. For this reason, AR provides a better assessment of fracture risk and is a more useful clinical tool for identifying patients most likely to benefit from therapy. The preferred fracture risk expression for use in clinical practice is AR denoted as the 10-year probability of fracture.

Fracture risk assessment tool — In 2008, a WHO task force introduced a Fracture Risk Assessment Tool (FRAX website), which estimates the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm) for **untreated** patients between ages 40 and 90 years using easily obtainable clinical risk factors for fracture (table 1) and femoral neck BMD (g/cm^2, using dual-energy x-ray absorptiometry [DXA]), when available [24,25]. DXA-equivalent femoral neck BMD derived from quantitative computed tomography (QCT) measurements may also be used with FRAX [29]; however, this is not recommended for use in clinical practice unless DXA is not available, due to greater radiation exposure and higher cost.

FRAX is based upon data collected from large prospective observational studies of men and women of different ethnicities and from different world regions in which clinical risk factors, BMD, and fractures were evaluated [12,28]. FRAX has been validated in 11 independent cohorts, mainly comprised of women [13]. The statistical power of this large dataset allows estimation of fracture probability from an individual's set of risk factors. The country-specific FRAX prediction algorithms are available for many countries online (FRAX website); click on Calculation Tool [25]. The FRAX calculator is also available on current versions of DXA software and as an app for smartphones. FRAX is a trademark of the WHO.

Results from a large prospective cohort study suggest that FRAX can similarly predict fracture in women currently or previously **treated** for osteoporosis [30]. In this analysis, the FRAX predicted risk and observed incidence of major osteoporotic fracture in both untreated and treated women were concordant. Only in the subset of women who were at highest risk for fracture and who were highly adherent to their osteoporosis treatment was the observed hip fracture incidence significantly less than the predicted risk. Thus, osteoporosis therapy may not preclude the use of FRAX for fracture prediction. However, FRAX does not appear to capture the change in fracture risk associated with therapy and should not be used to monitor individuals on therapy [31].

Other fracture risk assessment models are available, but most have not been validated in diverse populations, and they are not in widespread use [32-34].

Clinical application of fracture risk assessment — When country-specific fracture data and economic assumptions are used with FRAX, thresholds for cost-effective pharmacologic intervention can be calculated [28,35-40], allowing clinicians to identify patients likely to benefit from therapy better than currently available qualitative methods. Treatment guidelines based upon FRAX are likely to lead to more drug treatment in older patients with slightly low T-scores and high risk of fracture, with less use of drugs to treat younger patients with low T-scores and low risk of fracture.

In the United States, cost-effectiveness modeling suggests that the 10-year hip fracture probability at which treatment becomes cost-effective (intervention threshold) ranges from 2.5 to 4.7 percent for women and from 2.4 to 4.9 percent in

men, depending upon age and assuming annual treatment costs of $600 and a willingness-to-pay threshold of $60,000 per quality-adjusted life-year gained [35]. For a 70-year old woman initiating therapy, the intervention threshold is approximately 4 percent. Using similar willingness-to-pay thresholds but country-specific intervention costs, the intervention threshold in 70-year old women from other countries ranges from 4 to 9.1 percent [41].

Intervention thresholds vary based upon country-specific health economic data, such as fracture-related treatment costs and willingness-to-pay thresholds [24]. In most countries, the analysis is based upon five years of treatment with a bisphosphonate. The analysis in the United States was based upon the incidence of hip fracture in Caucasian postmenopausal women and the expected cost of generic alendronate (before the actual cost was known) [35,42]. Since the current cost of generic alendronate in the United States is less than the estimated cost, the fracture probability at which this treatment is cost-effective is presumably less than what was calculated. Conversely, the use of more expensive non-generic drugs increases the fracture probability at which treatment becomes cost-effective.

Guidelines for pharmacologic intervention based upon 10-year absolute fracture risk are reviewed in detail separately. (See "Treatment of osteoporosis in men", section on 'Candidates for therapy' and "Overview of the management of osteoporosis in postmenopausal women", section on 'Candidates for therapy'.)

Limitations — FRAX is a useful clinical tool for assessment of fracture risk. As with all clinical tools, however, there are some limitations. Limitations include lack of extensive validation in treated patients, limitation to four ethnicities (Caucasian, Black, Hispanic, Asian) in the United States, uncertainty regarding the range of error with fracture risk, and lack of validation with BMD measurements by technologies other than DXA [43,44] and QCT [29].

The FRAX algorithm uses femoral neck BMD (g/cm^2) for calculation of fracture probability in untreated patients. BMD input from non-hip sites and other hip regions of interest has not been validated with FRAX and is therefore not recommended [24]. For patients who have clinical risk factors for osteoporosis, low lumbar spine BMD, but normal femoral neck BMD, FRAX is likely to underestimate fracture risk. It is noteworthy that the FRAX estimation of major osteoporotic fracture does not include all osteoporotic fractures, since a substantial portion of fragility fractures are not at “major” skeletal sites [45]. Additional limitations, which may result in over- or underestimation of fracture risk in an individual patient, include dichotomous (yes or no) input for clinical risk factors that are associated with variable risk depending on dose and duration of exposure (eg, glucocorticoids) and lack of consideration of all risk factors (eg, multiple fractures, falls, bone turnover). While there is evidence that hip, vertebral, and humeral fractures appear to confer greater risk of subsequent fracture than fractures at other sites, quantification of this incremental risk in FRAX is not possible.

Thus, FRAX may underestimate fracture probability in individuals with a history of [43,44,46]:

- Low lumbar spine but normal femoral neck BMD
- Multiple fractures
- High-dose glucocorticoid exposure (prednisolone >7.5 mg/day or equivalent)
- Prevalent severe vertebral fractures
- A parental history of non-hip fragility fracture
- Diabetes mellitus

The magnitude by which FRAX may over- or underestimate fracture risk has been studied using large population databases, and procedures for adjusting FRAX probability have been proposed [47,48]. As an example, when there is discordance between lumbar spine and femoral neck BMD, the FRAX estimate for major osteoporotic fracture may be increased or decreased by one-tenth for each rounded T-score difference or offset between lumbar spine and femoral neck (eg, when the lumbar spine T-score is 1.0 less than the femoral neck T-score, the 10-year probability of major osteoporotic fracture can be increased by one-tenth) [47]. Another analysis using the United Kingdom General Practice Research Database showed that for patients exposed to high dose glucocorticoids (prednisolone >7.5 mg/day or equivalent), the 10-year probability of major osteoporotic fracture may be increased by 15 percent and the 10-year probability of hip increased by 20 percent [48]. With these modifications, the FRAX probability of fracture can be refined. However, these correction factors have not been computed for the majority of countries represented by FRAX, including the United States. Thus, they should not yet be applied to United States populations.

The clinician should appreciate that intervention guidelines with or without the use of FRAX provide only general clinical guidance. Osteoporosis treatment should remain individualized through shared decision-making between patient and clinician. (See "Treatment of osteoporosis in men", section on 'Candidates for therapy' and "Overview of the management

of osteoporosis in postmenopausal women", section on 'Candidates for therapy'.)

METHODS OF MEASUREMENT OF BMD — Low bone mineral density (BMD) is associated with increased risk of fracture, regardless of the technique used for measurement [12,15-21,49-60]. However, there are discrepancies in T-score values at different skeletal sites and with different technologies. The increase in fracture risk per 1.0 standard deviation (SD) decrease in BMD (fracture gradient) varies with the technique used and the skeletal site measured. Therefore, T-scores derived from different skeletal sites with different technologies are not interchangeable [10,61].

In clinical practice, dual-energy x-ray absorptiometry (DXA) is the only technology that can be used for diagnostic classification and is the most useful technology for monitoring serial BMD changes. However, other techniques measuring different skeletal sites have demonstrated the ability to predict the likelihood of fractures. Therefore, when BMD testing by DXA is not available, then fracture risk assessment may be made using other technologies (measuring lumbar spine, hip, or peripheral skeletal sites) in combination with consideration of clinical risk factors.

Dual-energy x-ray absorptiometry (DXA) — DXA measures bone mineral content (BMC, in grams) and bone area (BA, in square centimeters), then calculates "areal" BMD (aBMD) in g/cm^2 by dividing BMC by BA. DXA is the most widely used method for measuring BMD because it gives very precise and accurate measurements at clinically relevant skeletal sites (ie, those with major clinical consequences when a fracture occurs) and can be used for diagnostic classification, input with FRAX, and monitoring the response to therapy. The major disadvantages of DXA are that the instrument is large (not portable), more expensive than most peripheral technologies, and uses ionizing radiation, albeit in a very low dose.

Detailed information about DXA is found elsewhere. (See "Overview of dual-energy x-ray absorptiometry".)

Fracture prediction — Many studies have demonstrated that low BMD measured by DXA at any skeletal site (lumbar spine, hip, or forearm) can predict osteoporotic (fragility) fracture [15-18]. Overall, there is an approximately twofold increase in risk of such fractures for each SD decrease in BMD (table 3). As examples:

- In a prospective study of 9700 older women, 2680 of whom were followed for an average of 15 years, the risk of vertebral fracture was inversely related to bone density at all measurement sites [62]. The age-adjusted odds ratio (OR) of vertebral fracture for each SD decrease in DXA-measured BMD of the lumbar spine and total hip was 2.1 (95% CI 1.8-2.3) and 1.8 (95% CI 1.6-2.0), respectively.
- In a historical cohort study (mean observation 3.2 +/- 1.5 years) of 16,505 Canadian women, each SD decrease in DXA-measured BMD of the hip or lumbar spine was associated with an increased risk of osteoporotic fracture at any site (hazard ratio 1.8 [95% CI 1.7-2.0] for total hip and 1.5 [95% CI 1.4-1.6] for spine) [17].

Although low BMD at any skeletal site can predict osteoporotic fracture, site-specific measurements are generally better for their respective sites. As an example, hip BMD is superior to BMD measured at other skeletal sites in predicting hip fracture [12,15,17,19,20]. A meta-analysis of prospective cohort studies with over 90,000 person-years of observation found that every 1 SD decrease in BMD at the femoral neck in women was associated with a relative risk of 2.6 (95% CI 2.0-3.5) for hip fracture and 1.6 (95% CI 1.4-1.8) for all fractures. A 1 SD decrease in lumbar spine BMD was associated with a relative risk (RR) of 2.3 (95% CI 1.9-2.8) for vertebral fracture and 1.5 (95% CI 1.4-1.7) for all fractures [21].

There is a similar relationship between overall fracture, hip fracture, and femoral neck BMD in women and men [9,16,63].

High-trauma fractures (generally defined as fractures from motor vehicle accidents, sporting accidents, or falls from ladders or other raised surfaces) have traditionally been excluded from observational studies and clinical osteoporosis trials. Although the force to which bone is subjected varies with the level of trauma, the conventional view has been that even normal bone would fracture under most high-trauma conditions. Therefore, high-trauma fractures have not been considered a risk factor for osteoporosis [64]. (See 'Clinical risk factor assessment' below.)

However, evidence suggests that low BMD also increases the risk of high-trauma fractures [65,66]. As an example, in two large prospective cohort studies of community-dwelling older men and women, a 1 SD decrease in total hip BMD was associated with similarly increased risks of high- or-low trauma fractures (age-adjusted relative hazard [RH] 1.4 [95% CI 1.2-1.7] and 1.5 [95% CI 1.4-1.6] for high- and low-trauma fractures, respectively, in women and 1.5 [95% CI 1.2-2.0] and 1.7 [95% CI 1.5-1.9], for high-and low-trauma fractures, respectively, in men) [66].

Although the relationship between BMD and fracture appears to be similar regardless of the cause of fracture, the studies are limited by the broad definition of high-trauma fracture [64]. There is a level of force at which normal bone would

fracture, independent of BMD. The ability to accurately define traumatic fractures that are unlikely related to low BMD would clarify which patients with fracture require an evaluation for osteoporosis. Those who sustain fractures from a level of force at which normal bone would not ordinarily fracture require evaluation for osteoporosis (see "Screening for osteoporosis" and "Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women"). This relationship between force and fracture requires further investigation.

Follow-up BMD testing — DXA is commonly used to monitor the effects of pharmacologic therapy. Stability or an increase in BMD is considered to be a good response to therapy, whereas significant loss of BMD is cause for evaluation of factors contributing to suboptimal therapeutic effect and consideration of a change in treatment strategies. (See "Screening for osteoporosis", section on 'Repeat BMD measurements' and "Overview of the management of osteoporosis in postmenopausal women", section on 'Monitoring'.)

The value of repeat DXA in predicting fracture risk may be lower in older patients who are unlikely to experience further dramatic declines in BMD [67-69]. In the Study of Osteoporotic Fractures (SOF), a repeat BMD measurement performed a mean of eight years after the initial measurement did not improve the overall predictive value of hip, spine, or non-spine fracture risk in 4124 healthy community dwelling women 65 years and older [69]. However, these findings do not necessarily apply to younger women who may have accelerated bone loss (as in the early menopause), to women being treated for osteoporosis or low BMD, or to men [70,71].

Peripheral DXA (pDXA) — pDXA devices are dedicated portable instruments that use the same technology as DXA to measure BMD at peripheral sites, such as the forearm, calcaneus, or finger. Evaluation of fracture risk prediction with these devices is confounded by technical differences, variation in the definitions of the bone regions of interest measured, and lack of standardized reference databases for calculating T-scores. Nevertheless, low T-score values at peripheral sites measured by pDXA devices are associated with increased fracture risk [21,49].

Peripheral DXA cannot be used for diagnostic classification, other than with measurement at the distal 33 percent (one-third) radius site, since the WHO criteria for BMD classification do not apply to BMD at skeletal sites other than the lumbar spine, hip, and forearm [72]. Despite generally good precision with pDXA, it is not clinically useful to monitor therapy, since changes in BMD at peripheral skeletal sites in response to therapy are very slow [72].

Quantitative ultrasonography (QUS) — QUS does not measure BMD, but instead measures the transmission of ultrasound through accessible limb bones or the reflectance of the ultrasound waves from the bone surface. Parameters assessed by transmission ultrasound include broadband ultrasound attenuation (BUA), speed of sound (SOS), and calculated values such as quantitative ultrasound index (QUI) or stiffness index (SI). Reflectance ultrasound reports only SOS.

Potential advantages of QUS compared with measurement of BMD include lower expense, portability, and lack of radiation exposure. Measurements are most commonly made at the calcaneus (heel), a skeletal site that is composed primarily of cancellous bone, similar to the spine.

Fracture prediction — QUS is a good predictor of osteoporotic fracture risk [49-57,73]. As examples:

- In a large prospective study of 6189 postmenopausal women over age 65 years, QUS of the calcaneus predicted hip fracture as accurately as DXA of the calcaneus or femoral neck [52]. Each SD reduction in calcaneal BUA was associated with a doubling of the risk for hip fractures (relative risk [RR], 2.0; 95% CI 1.5-2.7).
- In a larger study of 14,824 patients that included younger women as well as men ages 42 to 82 years, calcaneal QUS also was a good predictor of total and hip fracture risk [51]. BUA predicted fracture risk in all subgroups of patients, with a relative risk similar to the study above.

In addition to predicting fracture risk, other studies have found that QUS is at least as good, and possibly better than clinical risk factors for predicting women at risk for osteoporosis [74,75].

In summary, QUS appears to be a good predictor of fractures in men and women, and is at least as good as clinical risk factors for identifying patients at high risk for osteoporosis. However, QUS cannot be used for diagnostic classification, since the WHO criteria were established based upon BMD measurement by DXA and cannot be used with FRAX. In addition, there are no studies showing reduction in fracture risk for patients selected for therapy based on QUS measurements, and QUS cannot be used to monitor response to therapy, because changes are too slow to be clinically useful. (See "Screening for osteoporosis" and "Clinical manifestations, diagnosis, and evaluation of osteoporosis in

postmenopausal women".)

Quantitative computed tomography — Quantitative computed tomography (QCT) measures volumetric BMD (vBMD) in mg/cm^3 at the spine and hip. Unlike DXA, QCT can isolate trabecular bone from its envelope of cortical bone. Some studies have suggested that QCT of the spine may be a slightly better predictor of fracture risk of the spine than anterior-posterior spine DXA [76,77], perhaps because of the important contribution of trabecular bone to vertebral body strength [78]. However, another study suggested that QCT of the spine is not superior to DXA of the hip in predicting non-spine fracture [79].

QCT-derived DXA-equivalent T-scores of the hip have been validated for diagnosing osteoporosis and osteopenia with the WHO criteria for BMD classification [29] but are not recommended for use in clinical practice unless DXA is not available, due to the level of radiation exposure and cost. A calculated aBMD of the hip derived from QCT measurements may be used for estimation of fracture risk with FRAX [80]. QCT may be clinically useful to monitor changes in BMD over time for some patients with structural abnormalities of the spine that preclude the use of DXA. It has a potential role in monitoring the therapeutic effects of anabolic agents or other types of drugs with novel mechanisms of action. At the present time, QCT is primarily a research tool that has been very helpful in improving our understanding of the pathogenesis of osteoporosis and the skeletal effects of drugs used to treat osteoporosis. It is more expensive, less reproducible, and requires a higher radiation dose than DXA.

New and emerging technologies — Although BMD measured by DXA is the most common method for assessing fracture risk in clinical practice, it has some limitations. DXA measures aBMD, rather than vBMD. In addition, it cannot distinguish between cortical and trabecular bone, cannot assess bone microarchitecture, and is not the only predictor of fractures. Thus, new technologies and non-BMD DXA measurements have been developed that allow noninvasive assessment of bone strength. As examples:

- Trabecular bone score (TBS) is a commercially available US Food and Drug Administration (FDA)-approved software add-on for late generation DXA systems that uses data derived from lumbar spine DXA images to generate a gray-level textural index. TBS is associated with vertebral, hip, and major osteoporotic fracture risk in postmenopausal women and with hip fracture risk and major osteoporotic fracture risk in men over age 50 years [81]. TBS should not be used alone to initiate therapy and is not useful to monitor bisphosphonate therapy in postmenopausal women with osteoporosis. It is associated with major osteoporotic fracture risk in postmenopausal women with type 2 diabetes mellitus and can be used with the FRAX algorithm to estimate fracture risk.

- High resolution peripheral QCT (HR-pQCT), high resolution MRI (HR-MRI), and microMRI measure structural bone properties at peripheral sites (distal radius, tibia) in vivo. Alterations in microarchitecture as detected by these techniques have been associated with increases in fracture risk [82-85].

- Hip structural analysis (HSA) uses information about bone geometry and mass distribution obtained from DXA scans of the hip to calculate parameters that include hip axis length (HAL), neck-shaft angle (NSA), cross-sectional area (CSA), outer width (OD), section modulus (SM), cross-sectional moment of inertia (CSMI), and buckling ratio (BR) [86]. HAL derived from DXA is associated with hip fracture risk in postmenopausal women, while NSA, CSA, OD, SM, and CSMI derived from DXA should not be used to assess hip fracture risk [87]. None of these parameters should be used to initiate or monitor treatment.

- Structural engineering models (SEMs) of the hip integrate DXA-derived hip data with applied forces to estimate hip fracture risk [86].

- Finite element analysis (FEA) uses computer models of images and data from QCT of the spine or hip to assess bone strength [88]. QCT-based FEA can be used to predict vertebral fracture in postmenopausal women and is comparable to spine DXA in predicting vertebral fractures in men [89]; it is also comparable to hip DXA in predicting hip fractures in postmenopausal women and older men. FEA cannot be used to diagnose osteoporosis, initiate therapy, or monitor therapy.

While all of these technologies have provided insight into skeletal properties other than BMD that determine bone strength, their role in clinical practice has not been defined. These techniques are used primarily in research settings.

SKELETAL SITE TO MEASURE — Fracture risk can be predicted by measurement or estimation of bone mineral density (BMD) at many skeletal sites with a variety of technologies. Although BMD measurements at peripheral skeletal sites

predict global fracture risk (ie, the risk of fracture at any skeletal site) as well as BMD measurement at the hip or spine [18,90], the risk for fracture at a particular skeletal site is best estimated by measuring BMD at that skeletal site [91-94].

The International Society for Clinical Densitometry (ISCD) recommends that the World Health Organization (WHO) criteria be applied to BMD measured by dual-energy x-ray absorptiometry (DXA), using the lowest T-score of the lumbar spine (preferably L1-L4), femoral neck, or total proximal femur. If BMD cannot be measured at either of these skeletal sites due to structural abnormalities, such as osteoarthritis or surgical artifact, then the distal 33 percent (one-third) radius should also be measured and considered for diagnostic classification [72].

We recommend following ISCD recommendations (DXA of the lumbar spine and hip). However, the lumbar spine is less useful for BMD measurement in older individuals, in whom structural abnormalities, such as degenerative arthritis and disc disease, commonly result in BMD increases. In such patients, measurement of the hip alone could be sufficient. (See "Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women", section on 'Site of measurement' and "Treatment of osteoporosis in men".)

In addition, it is important to note that Fracture Risk Assessment Tool (FRAX) was designed to calculate fracture probability with femoral neck BMD measured by DXA. The validity of FRAX with BMD measured at other skeletal sites and using other technologies (other than quantitative computed tomography [QCT] when DXA is not available) has not been determined and therefore is not recommended. (See 'Clinical application of fracture risk assessment' above.)

CLINICAL RISK FACTOR ASSESSMENT — Most fractures occur in patients who do not have a World Health Organization (WHO) classification of osteoporosis according to a T-score of -2.5 or less. Although patients with osteoporosis are at the highest risk of fracture, there are more fractures in patients with low bone mass or osteopenia (T-score between -1.0 and -2.5) because there are so many more patients in this category [7,95,96]. Therefore, assessment of clinical risk factors that are independent of bone mineral density (BMD) is important for fracture prediction.

Some of these factors in Caucasian women and men include advancing age, previous fracture, glucocorticoid therapy, a family history of hip fracture, poor visual capacity, low body weight, neuromuscular disorders, and smoking (table 1) [10,97,98]. Similar risk factors were identified in a prospective study of 1435 Chinese women [23].

Many of these risk factors are easily discernible from a routine history and physical examination; taken together they are predictive of future hip fracture, even in the absence of BMD measurement [99,100]. Advancing age and previous personal history of fracture are two of the most important BMD-independent risk factors for fracture.

Clinical risk factor assessment alone may be considered for fracture prediction in world regions without access to any BMD technologies. The Fracture Risk Assessment Tool (FRAX website) model allows estimation of 10-year probability of hip fracture and major osteoporotic fractures using clinical risk factors alone or in combination with femoral neck BMD. (See 'Fracture risk assessment tool' above.)

Advanced age — For any given T-score the risk of fracture is higher with advancing age (figure 1) [101].

Personal history of fracture as an adult — A history of a fragility (low-trauma) fracture is another important risk factor for subsequent fracture in men and women [62,102-106]:

- A meta-analysis of 11 prospective cohort studies of fracture risk in men or women with prior fracture reported increased risks of any fracture (relative risk [RR] 1.8, 95% CI 1.6-1.9), osteoporotic fracture (RR 1.8, 95% CI 1.6-1.9), and hip fracture (RR 1.6, 95% CI 1.3-2.0) in both men and women, even after adjustment for BMD [104].
- In a prospective cohort study of 4005 Australian men and women followed for 16 years, the RR of subsequent fracture in women with any initial low-trauma fracture (after age 60 years) was 2.0 (95% CI 1.7-2.2) and for men was 3.5 (95% CI 2.7-4.5) [102].
- In a longitudinal study (SOF) of 9700 older (age >65 years at baseline) women, 2680 of whom were followed for an average of 15 years, the absolute risk (AR) of a new vertebral fracture in women with previous vertebral fracture ranged from 25 to 50 percent, depending upon T-score [62]. The risk of new vertebral fracture was greatest in women with a total hip T-score ≤-2.5 and a previous vertebral fracture (absolute risk [AR] 56 percent, 95% CI 44 to 69 percent). (See 'Expression of fracture risk' above.)

In women, a history of a high-trauma fracture may also be a risk factor for subsequent fracture [66]. In a nine-year study of 8022 women participating in SOF, women with a previous history of high- and low-trauma nonspine fractures had a

similarly elevated risk of subsequent fracture compared with women who had not had such fractures [66]. The risk of a subsequent fracture was 34 percent (95% CI 7-67) and 31 percent (95% CI 20-43) greater among women with a history of high- and low-trauma fracture, respectively.

Glucocorticoid therapy — A retrospective cohort study in 244,235 oral glucocorticoid users in the United Kingdom General Practice Research Database showed a dose-dependent relationship between chronic glucocorticoid use and fracture risk, with high doses (prednisolone 7.5 mg/day or greater) having the highest risk [107]. Low doses of glucocorticoids (prednisolone less than 2.5 mg/day) were also associated with increased fracture risk. (See "Pathogenesis, clinical features, and evaluation of glucocorticoid-induced osteoporosis" and "Prevention and treatment of glucocorticoid-induced osteoporosis".)

History of fragility fracture in a first-degree relative — Parental history of hip fracture is associated with a twofold increased risk of hip fracture in women, regardless of BMD [99].

Low body weight — Low body weight (less than 58 kg [127 lb]) is associated with increased risk of osteoporosis and fractures, possibly related to small bone size [108-111]. Weight loss after age 50 years in women and increased height also raise the risk of hip fracture, while weight gain decreases it [109,112,113].

The mechanism of weight loss may influence the effect on bone physiology. In one small, randomized trial, subjects who lost weight by calorie restriction had decreases in total hip BMD, whereas subjects who lost the same amount of weight via exercise without reduced caloric intake had no changes in BMD [114].

Cigarette smoking — Meta-analyses have shown that cigarette smoking is associated with reduced BMD and increased risk of fracture [115,116]. The risk of fracture was increased with a smoking history and current smoking, but was higher for current smokers.

Excessive alcohol consumption — The risk of fracture with excessive alcohol intake is dose dependent [117]. A meta-analysis of case-control and prospective cohort studies showed that alcohol consumption in excess of two drinks (approximately 28 g of pure alcohol) per day is associated with an increased risk of hip fracture (RR 1.39, 95% CI 1.08-1.79) [118].

Medical diseases — Many medical diseases are associated with low BMD and an increased risk of fracture, either due to underlying inflammation, malabsorption, renal excretion of calcium, or medications used to treat the diseases. As examples:

- Rheumatoid arthritis. (See "Overview of the systemic and nonarticular manifestations of rheumatoid arthritis".)
- Inflammatory bowel disease. (See "Metabolic bone disease in inflammatory bowel disease".)
- Celiac disease. (See "Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults", section on 'Metabolic bone disease'.)
- Cystic fibrosis. (See "Cystic fibrosis: Clinical manifestations and diagnosis", section on 'Musculoskeletal disorders'.)
- Previous hyperthyroidism. (See "Bone disease with hyperthyroidism and thyroid hormone therapy".)
- Type 1 and 2 diabetes. (See "Bone disease in diabetes mellitus".)
- Renal disease. (See "Overview of chronic kidney disease-mineral bone disease (CKD-MBD)".)

  End-stage renal disease is associated with an increased risk of fracture. In addition, moderate degrees of renal insufficiency (as estimated in patients with a stable serum creatinine) have been reported to be associated with an increased fracture risk in one study [119], but not in another [120].
- Sickle cell disease. (See "Bone and joint complications in sickle cell disease".)

Other risk factors — Risk factors in addition to those described above (table 1) include the following:

- Vitamin D deficiency.
- Reduced functional mobility, recurrent falls, or use of walking aids. (See "Falls in older persons: Risk factors and patient evaluation".)

- Many drugs, including androgen deprivation agents, aromatase inhibitors, proton pump inhibitors, selective serotonin reuptake inhibitors (SSRIs), thiazolidinediones, and anticonvulsants. (See "Side effects of androgen deprivation therapy", section on 'Osteoporosis and bone fractures' and "Drugs that affect bone metabolism".)
- Dementia.
- Poor health/frailty.
- Previous fracture between the ages of 20 and 50 years. (See "Epidemiology and etiology of premenopausal osteoporosis", section on 'Fractures'.)
- A previous history of breast cancer. (See "Patterns of relapse and long-term complications of therapy in breast cancer survivors", section on 'Musculoskeletal'.)

Possible risk factors

- Depression has been associated with an increased risk of fracture in some studies [121]. However, the relationship between depression and fracture is likely complex. Individuals with depression tend to have other risk factors for fracture, including medication use (SSRIs), increased frequency of falling, hypercortisolism, and lifestyle factors (smoking, alcohol). (See 'Other risk factors' above.)
- Mild asymptomatic hyponatremia (serum sodium <135 mEq/L) was associated with an increased risk of fall-related fractures (adjusted odds ratio [OR] for fracture 4.2, 95% CI 2.2-7.7) in a case-control study [122]. In the majority of cases, hyponatremia was either drug-induced (diuretics, SSRIs, and antiepileptic drugs) or was due to the syndrome of inappropriate antidiuretic hormone secretion. (See "Drugs that affect bone metabolism".)
- Aortic calcification on computed tomography (CT) scan (a marker of atherosclerosis) [123].
- Elevated markers of inflammation [124,125].
- High dietary retinol intake, which some but not all studies suggest increases fracture risk. (See "Drugs that affect bone metabolism".)
- Sedentary lifestyle [126].
- Vitamin B12 deficiency (pernicious anemia). (See "Etiology and clinical manifestations of vitamin B12 and folate deficiency".)
- High homocysteine concentrations, which are associated with an increased risk of fracture in some but not all studies [127-134].
- Consumption of large amounts of caffeine: The association between excess caffeine and increased fracture risk has been variably reported as a definite association [99], no association [135,136], and an association only if the patient does not drink milk [137].
- Carbonated beverages may be associated with adverse skeletal effects in adolescents, possibly due to the displacement of nutritious foods and beverages, but the impact in older women is unclear. In one report, modest intake of carbonated beverages did not have adverse effects on BMD [138], while in another, cola drinks (but not other carbonated beverages), were associated with lower bone density [139]. (See "Calcium requirements in adolescents".)

Bone turnover markers (BTMs) — Measurements of BTMs may provide information about expected rates of bone loss and fracture risk that cannot be obtained from measurements of BMD (figure 2) [140,141]. Elevated BTMs have been demonstrated to be associated with increased risk of vertebral and nonvertebral fracture, independently of BMD, suggesting that BMD combined with a BTM may improve fracture prediction (figure 3) [142,143]. (See "Use of biochemical markers of bone turnover in osteoporosis".)

However, the relationship between BTMs and fracture risk has not been validated in all studies. As examples:

- In a subset of placebo patients in the Multiple Outcomes of Raloxifene (MORE) study, none of the BTMs (bone-specific alkaline phosphatase, osteocalcin or urinary C-telopeptide) that were measured influenced fracture risk [144].

- In an observational study of 225 postmenopausal women followed for a median of 16.2 years, BTMs (osteocalcin, alkaline phosphatase, and urinary hydroxyproline) did not predict any type of osteoporotic fracture [68].

While the use of BTMs in clinical trials has been helpful in understanding the mechanism of action of therapeutic agents, their role in the care of individual patients is not well established. Potential roles of BTMs in clinical practice include prediction of fracture risk, monitoring response to therapy, and as an aid in selection of drug for treatment [145]. It is not clear which specific BTM is most useful for specific clinical situations. Biologic and within individual variability in BTM values have confounded their widespread use in clinical practice.

SUMMARY AND RECOMMENDATIONS — Bone mineral density (BMD) and clinical risk factors may be combined to provide a better estimate of fracture risk than BMD or clinical risk factors alone.

Fracture prediction

- The Fracture Risk Assessment Tool (FRAX website) estimates the 10-year probability of hip fracture and major osteoporotic fracture for an untreated patient (40 to 90 years of age) using femoral neck BMD (g/cm^2) and easily obtainable clinical risk factors for fracture (table 1). (See 'Fracture risk assessment tool' above.)
- FRAX may be calibrated for each country using country-specific fracture data and mortality data (when available), then used with country-specific economic assumptions to develop treatment guidelines with thresholds for cost-effective pharmacologic intervention. (See 'Clinical application of fracture risk assessment' above.)
- With the use of the FRAX model, it is anticipated that intervention will be more effectively targeted to those at highest risk of fracture, ie, older patients with slightly low T-scores and high risk of fracture will be selected for drug therapy, while fewer younger patients with low T-scores and low risk of fracture will be treated. (See 'Clinical application of fracture risk assessment' above.)
- Clinical risk factor assessment alone may be considered for fracture prediction in world regions without access to any BMD technologies. The FRAX model allows estimation of 10-year probability of hip fracture (and major osteoporotic fractures) using clinical risk factors alone or in combination with femoral neck BMD. (See 'Clinical risk factor assessment' above.)

Bone mineral density

- Dual-energy x-ray absorptiometry (DXA) measurements of hip or spine or peripheral measurements of BMD using different validated techniques can be used to predict fracture. However, T-scores derived from different skeletal sites with different technologies are not interchangeable. (See 'Methods of measurement of BMD' above.)
- We suggest DXA measurement of BMD at the hip and lumbar spine. When either the hip or lumbar spine is not a valid skeletal site for BMD measurement, then the 33 percent (one-third) radius should be measured. In some patients, measurement of the hip alone could be sufficient. (See 'Skeletal site to measure' above.)

Assessment of clinical risk factors

- The most robust non-BMD risk factors are age and prevalent fracture. Other validated BMD-independent risk factors for fracture include long-term glucocorticoid therapy, parental history of hip fracture, cigarette smoking, and excess alcohol intake (table 1). (See 'Clinical risk factor assessment' above.)

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Topic 2061 Version 21.0

GRAPHICS

Clinical risk factors for fracture

Advancing age
Previous fracture
Glucocorticoid therapy
Parental history of hip fracture
Low body weight
Current cigarette smoking
Excessive alcohol consumption
Rheumatoid arthritis
Secondary osteoporosis (eg, hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease)

Data from: Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Int 2005; 16:581.

Graphic 76445 Version 3.0

Relative risk versus absolute risk estimates of fracture

Age	Hip T-score	Relative risk	10-year fracture probability, percent
50	-2.5	17.6	1.7
80	-2.5	17.6	11.5

Relative risk compared to age-matched women with normal BMD.
(RR per SD change in BMD)$^{\text{T-score Difference}}$ = $(2.6)^{2.5}$ = 17.6.

BMD: bone mineral density; RR: relative risk; SD: standard deviation.

10-year fracture probability from Swedish National Bureau of Statistics.
Data from: Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996; 312:1254 and Kanis JA, Johnell O, Oden A, et al. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporosis International 2001; 12:989.

Graphic 67119 Version 2.0

Relative risk of fracture for each age-adjusted standard deviation decrease in BMD

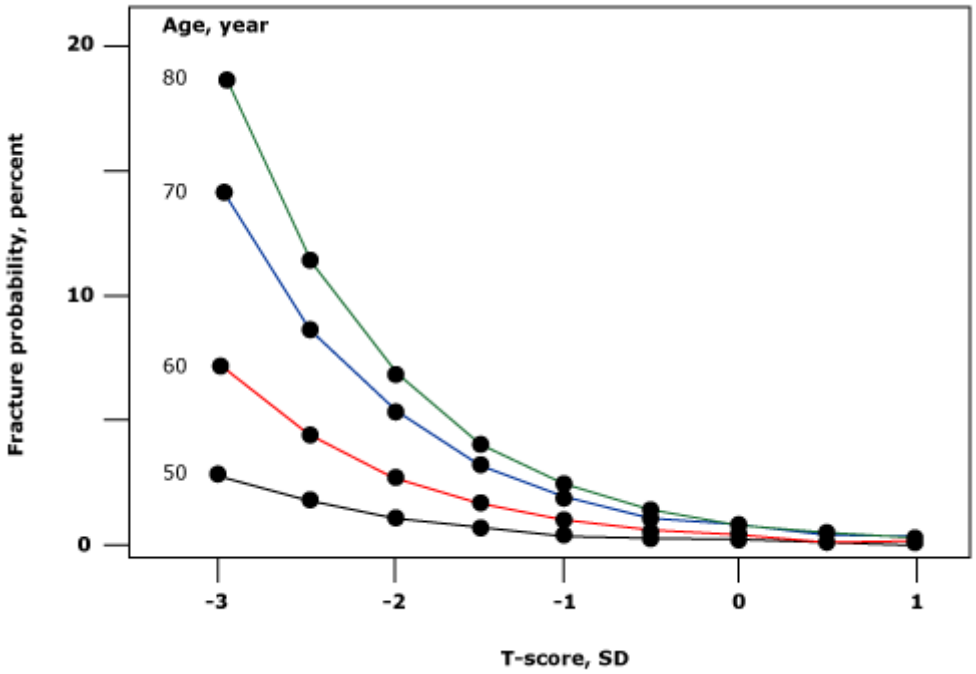
Skeletal site of BMD measurement	Hip fracture	Vertebral fracture
Distal radius	1.8	1.7
Proximal radius	2.1	2.2
Calcaneus	2.0	2.4
Spine	1.6	2.3
Femoral neck	2.6	1.8

BMD: bone mineral density.

Data from: Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996; 312:1254.

Graphic 51324 Version 3.0

Ten-year fracture probabilities according to BMD T-score and age



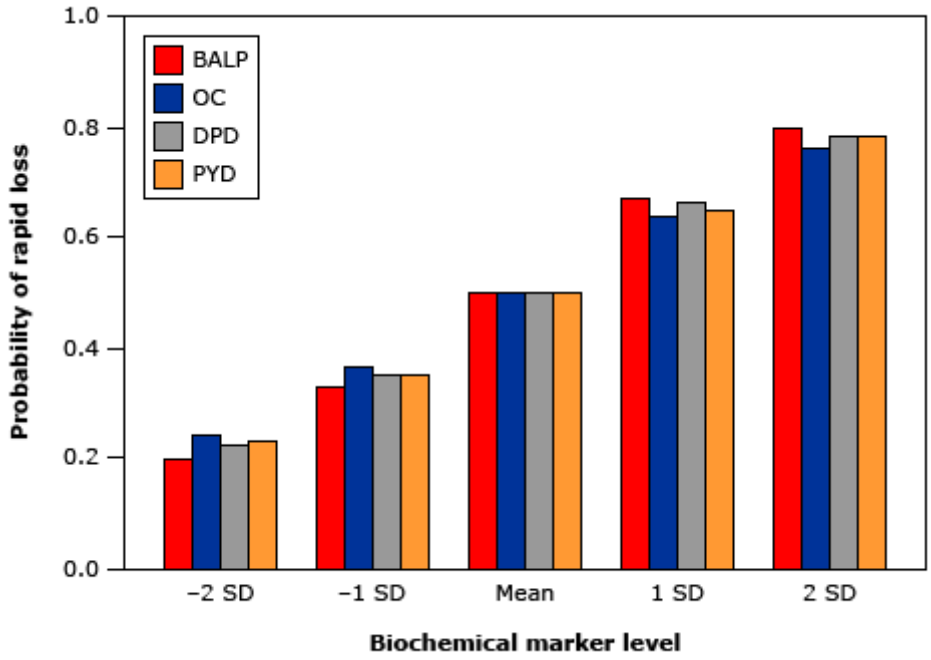
The relationship between BMD femoral neck T-score, age and hip fracture probability in women. The probability of hip fracture for any given T-score is higher with increasing age.

BMD: bone mineral density; SD: standard deviation.

Data from: Kanis JA, Johnell O, Oden A, et al. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int 2001; 12:989.

Graphic 54599 Version 2.0

High bone turnover is predictive of rapid bone loss

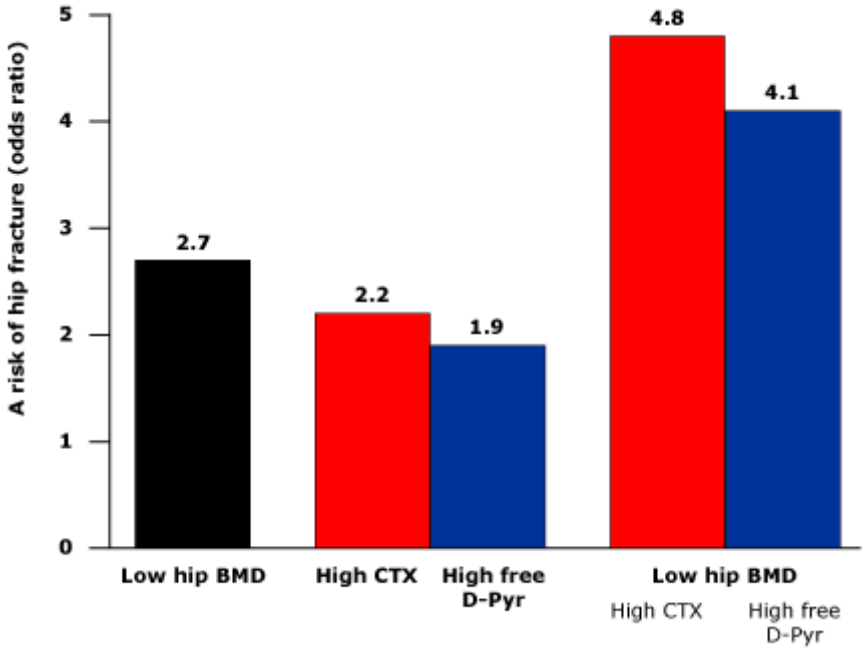


The probability of rapid loss was calculated from the corresponding logistic regression equation for each marker. At each level, from left to right, the markers were: BALP (red bars), OC (blue bars), DPD (gray bars), and PYD (orange bars). The means and SDs were based on all 199 samples.

SD: standard deviation; BALP: bone-specific alkaline phosphatase; OC: osteocalcin; DPD: free deoxypyridinoline; PYD: free pyridinolines.

Graphic 71125 Version 4.0

BMD and bone turnover markers are independent predictors of hip fracture risk



Low BMD was defined according to the WHO guidelines, ie, by a value 2.5 SD or more below the young-adult mean (T-score ≤2.5). High bone resorption was defined by CTX or free D-Pyr values higher than the upper limit (mean +2 SD) of the premenopausal range. Women with both low hip BMD and high bone resorption were at a higher risk of hip fracture than women with either low hip BMD or high bone resorption.

BMD: bone mineral density; CTX: C-telopeptide; D-Pyr: free deoxypyridinoline; SD: standard deviation; WHO: World Health Organization.

Graphic 77540 Version 2.0

Contributor Disclosures

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Conflict of interest policy