Clinical fractures beyond low BMD

The risk of fractures is multifactorial and is related to the ability of bone to resist fracturing, which depends on its material and structural properties, and on the intensity, frequency and impact of trauma. Low BMD is a major determinant of bone strength and fracture risk. However, most patients with a fracture have no osteoporosis and BMD explains <50% of bone strength and fracture risk. Beyond BMD, bone strength can be calculated by analysis of 2D and 3D structural images of the bone, but this is not yet part of daily clinical practice. Fracture risk can be evaluated by integrating BMD with systematic evaluation of clinical risk factors, such as in the fracture risk assessment tool (FRAX) case finding algorithm (age, personal and family history of clinical fractures, life style, diseases and medications). Clinical risk factors, not included in FRAX, are fall risks, the number and timing of previous clinical fractures, the presence, number and severity of morphometric vertebral fractures and the dose of glucocorticoids. These have been included in other case finding tools, such as the Garvan Fracture Risk Calculator, the Fracture Risk in Glucocorticosteroid Users and the Maastricht Fracture Risk Nomogram. Further refinement of case finding algorithms will be needed to integrate BMD, bone strength calculations and clinical risk factors into a single algorithm for fracture risk prediction, that can be used in daily practice.

KEYWORDS: BMD ■ bone imaging ■ bone strength ■ fracture risk ■ FRAX

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the effects of BMD and bone strength on fracture risk based on a review
- Describe the FRAX case-finding algorithm for fracture risk based on that review
- Describe clinical algorithms other than FRAX for determining fracture risk based on that review

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The life-time risk of fracture for a white woman of 50 years of age is >50% and in men >20% [1], however this varies between populations [2]. The incidence of most but not all fractures increases exponentially with advancing age [3]. Fractures incur significant costs and cause considerable disability and morbidity, depending on fracture location, age and sex [4]. After a fracture, the risk of mortality, morbidity and subsequent fracture is increased and is highest within the first years after a fracture [5–10].

The bone's resistance to fracture is determined by BMD and many other components. These include bone macroarchitecture (geometry), microarchitecture (trabecular number, thickness and connectivity), cortical porosity, matrix properties (collagen cross-linking and noncollageneous proteins), tissue mineralization density, crystal characteristics, damage accumulation (crack-initiation and crack-growth toughness) and damage repair [11–13].

The etiology of fractures is thus multifactorial (Figure 1). In this article, we reviewed structural characteristics of the bone that contribute to bone strength and clinical risk factors that contribute to fracture risk, independent of BMD.

BMD & fracture risk

At present, diagnosis of osteoporosis is based on measurement of areal BMD (aBMD) by dual-energy x-ray absorptiometry (DXA). DXA is a projectional imaging technique that measures the relative tissue absorption of a dual energy x-ray spectrum and provides areal density as g/cm^2. Since its introduction in 1987, DXA has become the most widely accepted means of measuring BMD.

Many studies have demonstrated that a decrease in aBMD is a risk factor for fractures. Highest fracture rates are observed among women with osteoporosis (as defined on the basis of aBMD alone) [14,15]. In a large meta-analysis of prospective cohort studies in women (mean age 53–73 years, average follow-up of 0.7–26 years), the relative risk for forearm, hip, vertebral and all other fractures increases 1.6–2.5-fold per standard deviation (SD) decrease in aBMD [16,17]. Site-specific measurements of aBMD at the lumbar spine and hip are better predictors of fracture at those sites than measurements at other skeletal sites [16,18,19].

Dual-energy x-ray absorptiometry is now considered to be the gold standard for measuring the aBMD component of fracture risk in daily practice. Measurement of BMD has contributed to the epidemiology, pathophysiology, detection and treatment of patients at high risk for fractures. However, the interpretation of BMD has several limitations.

First, although fracture risk is highest in patients with lowest aBMD (i.e., with osteoporosis), most patients with a fracture do not have

osteoporosis at the time of fracture. In a large survey of postmenopausal women, 82% of patients with fractures had T-scores better than -2.5 SD using peripheral measurement devices (in the heel, forearm or finger) [14]. In patients with a recent hip fracture, which is considered a major osteoporotic fracture [20], only 41% had a femoral neck aBMD T-score <-2.5 [21]. In patients with repeat fractures, which account for 25–40% of all fractures after the age of 50 years, only 33% of men and 50% of women had osteoporosis [22]. In patients with a recent nonvertebral fracture, 25% had also a vertebral fracture, more than half of which were found in patients without aBMD osteoporosis [23]. In patients with a recent clinical fracture, 27% had newly diagnosed secondary osteoporosis and metabolic bone diseases, of which 57% of men and 49% of women had no osteoporosis [24].

Second, less than 60% of the variation in femoral whole-bone strength is attributable to variations in BMD [25]. Changes in BMD during treatment with antiresorptive drugs are related to fracture risk reduction [26], but they only explain little of their antifracture effect [27], except with strontium ranelate [28].

Third, the measurements are 2D so larger bones may have higher aBMD than smaller bones because of differences in bone depth [29]. The bone with the lower BMD may not have gained less or lost more bone. In addition, DXA also does not distinguish cortical and cancellous bone, nor do changes in aBMD provide information regarding the morphological basis of that change.

Fourth, the relation between BMD and fracture risk is strongly dependent on clinical risk factors. For example, the 5-year hip fracture risk is <5% at any BMD below the age of 65 years, but in women older than 65 years, varies between <5% at a femoral neck (FN) T-score of >-2.0–20% at a FN T-score of -3.5 [30]. Similar relations were found between 5-year vertebral fracture risk, age and BMD. The relation between the 5-year risk of low-trauma nonvertebral fractures and BMD also raised with age, but not as much as for hip and vertebral fractures [30].

These limitations of BMD have generated extensive research in methods to calculate bone strength and predict fracture risk.

Alternative measures of bone strength

In view of the limitations of measuring BMD, analytical methods have been developed to assess biomechanical components of bone, based on structural characteristics of bone. Analyses of bone structure to calculate bone strength have been performed with 2D projectional techniques including DXA, plain radiography or high resolution digital radiography (HRDR), and 3D imaging methods such as quantitative computed tomography (QCT) and MRI and with quantitative ultrasound techniques (**Box 1**).

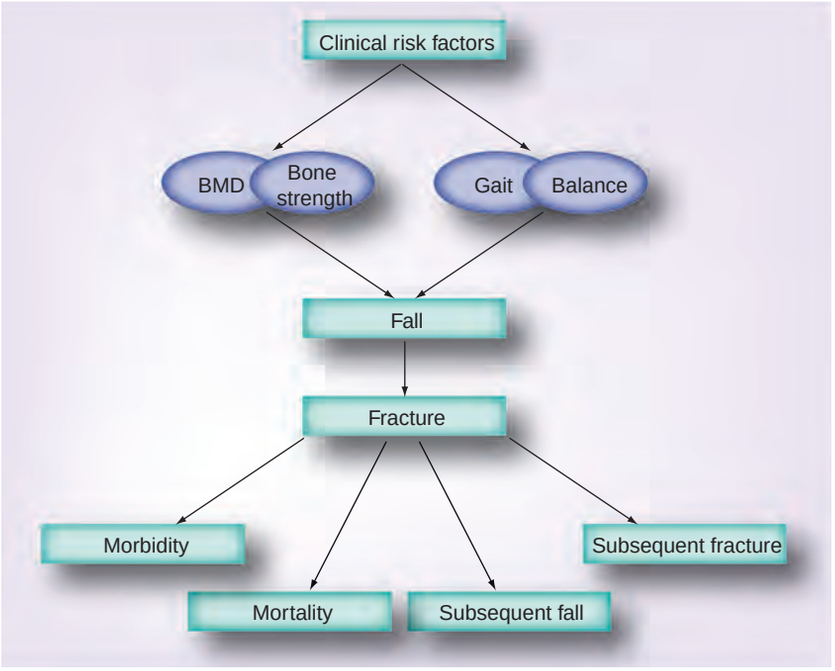

Figure 1. Multifactorial etiology and consequences of fractures in women and men older than 50 years.

Macroarchitecture has been evaluated by measuring hip axis length (HAL), femoral neck axis length (FNAL), femoral neck/shaft angle (FSA), cross-sectional moment of inertia (CSMI), moment of inertia (MI), moment side fall on 2D images of digitized radiographs and DXA, and on 3D imaging by CT and MRI [31–40]. Microarchitecture can be evaluated on 2D radiographs, which enables texture analysis techniques to be applied for assessment of trabecular architecture. Volumetric 3D cortical and trabecular microarchitecture can be evaluated by CT and MRI, which allows to study cortical and trabecular bone separately [41]. Structural analysis is still in experimental phase and currently not routinely used in daily practice.

Structural analysis of 2D images

Bone densitometry

Recent advances in DXA include software that automatically calculates several proximal femoral structural parameters, HAL, femoral neck cross-sectional area (CSA), MI, and FSA. HAL is the distance along the femoral neck

Box 1. Imaging modalities of the skeleton and calculation of biomechanical parameters.

Imaging

- 2D projectional techniques
  - Dual-energy x-ray absorptiometry
  - Plain radiography
  - High-resolution digital radiography
- 3D imaging
  - Quantitative computed tomography
  - MRI
- Other
  - Quantitative ultrasound

Analyses

- Macroarchitecture
  - Hip axis length
  - Femoral neck axis length
  - Femoral neck/shaft angle
  - Cross-sectional area
  - Cross-sectional moment of inertia
- Microarchitecture
  - 2D radiographs: trabecular texture analysis
  - True volumetric density (mg/cm^3)
  - Volumetric 3D cortical and trabecular microarchitecture of total bone and cortical and trabecular bone separately
  - Finite element analysis

axis from the base of the greater trochanter to the pelvic brim. CSMI is a measure of how the bone is distributed in the femoral neck. These structural parameters, which compare reasonably with similar measurements obtained from volumetric QCT, can be combined with subject height, weight, and age data to calculate the femoral strength index (FSI) [33]. In a study comparing hip-fracture patients with control subjects older than 50 years, fracture prediction was marginally improved by combining the T-score with the HAL and FSI compared with the T-score alone. Femoral neck CSMI, CSA and FSA were not found to be independent predictors of hip fracture [33]. These findings are in line with the data from Wang *et al.* who demonstrated that there was no difference in aBMD, HAL or FSA between patients with hip fractures and controls [42]. Recently, it was reported that volumetric dual-energy x-ray absorptiometry (VXA), that uses a DXA system to reconstruct the proximal femur from four DXA scans, provided good correlations with QCT with regard to HAL and CSA [43]. Possibly this new technique may contribute to improve prediction of hip fractures with DXA. In addition, vertebral fracture assessment by DXA provides an image of the thoracic and lumbar spine for the purpose of detecting vertebral fracture deformities. Identification of a previously unrecognized vertebral fracture contributes to the assessment of fracture risk, and treatment decisions [44].

Plain radiography

Plain radiographs are used to diagnose fractures. The presence of a low-trauma vertebral or nonvertebral fracture is evidence of reduced bone strength, independent of BMD. Subsequent fracture risk is related to the number of any previous fracture [101] and to the presence, severity and number of vertebral fractures [45,46]. While most nonvertebral fractures are easy to diagnose, two out of three vertebral fractures do not present with the clinical signs and symptoms of a fracture, and often go undiagnosed until imaging of the spine is performed, but are often disregarded or missed when x-rays of the spine are available. Imaging of the spine enables to SQ evaluate vertebral heights, for which the Genant score is often used for scoring.

Visual inspection of radiographs is not adequate to quantify bone loss. It is estimated that bone loss of less than 20–40% cannot been detected on plain radiographs [47].

Plain radiographs have also been used to evaluate trabecular texture architecture. Fractal analysis of trabecular bone which reflects anisotropy [48], has good correlations with 3D microcomputed tomography [49]. In patients with a history of fracture, radiographic texture analysis (RTA) provided an estimate of bone fragility independent of and complementary to BMD measurement and age [50,51].

Using digitized radiographs of the hip, active shape modeling (ASM) is a method that integrates the measurements of the shape of the proximal femur, femoral neck width and femoral neck length [52]. The accuracy of discrimination between patients with and without a hip fracture was improved by combining ASM modes with femoral neck or intertrochanteric BMD [52].

3D imaging

Quantitative computer tomography

Quantitative computer tomography measurements are reported as true volumetric density (mg/cm^3). Volumetric QCT can analyze both densitometry and geometrical components either of the entire bone or its cortical and trabecular components separately, not restricted by the limitations inherent to projectional radiographic and DXA examinations (Figure 2) [53,54]. Biomechanical testing of cadaver hips has demonstrated that strength is related to trabecular

and cortical bone, and that strength prediction can be enhanced by combining BMD with geometric characteristics, including CSA, FNAL using QCT [55].

Volumetric QCT and MRI enables *in vivo* assessment of subregional differences in the trabecular pattern and density. The established engineering method of finite element analysis (FEA) modeling can be used to improve QCT estimation of bone strength. The QCT data are converted into 'voxel' finite element models to yield measures of bone strength [56]. Highly automated finite element models were superior to correlation-based QCT methods in predicting vertebral compressive strength [57].

Finite element analysis also offers the possibility of directly predicting the effect of different osteoporosis treatments on bone strength. It was demonstrated that both teriparatide and alendronate over an 18-month period improved vertebral strength by increasing volumetric density, but the effect on vertebral strength was more pronounced with teriparatide, which preferentially improved the density and strength of the trabecular component [58]. This enhanced effect of teriparatide was only evident on finite element modeling and not on BMD measurement by DXA [58]. In a recent study, FEA demonstrated that teriparatide treatment leads to an increase in vertebral bone strength of up to 30% during compression and bending [59]. Based on theoretical implications from a 2-year clinical trial in postmenopausal women treated with alendronate, parathyroid hormone or their combination, calculation of the biomechanical fracture threshold may lead to new insights and advances in the assessment and treatment of osteoporosis and fracture risk reduction [53].

With the recent introduction of a new generation high-resolution 3D peripheral QCT system, direct quantification of structural bone parameters has become feasible with a resolution of 80 µm (FIGURE 2) [60]. It allows measurements of the distal radius and tibia *in vivo* with low radiation (3 µ Sievert), and is a promising technique for evaluation of changes in architecture of trabecular architecture and in cortical size and porosity [61,62]. In a case–control study involving 101 women with prevalent fragility fracture and 101 age-matched controls, from the OFELY cohort it has recently been shown that FEA parameters at the radius and tibia derived with a high-resolution 3D peripheral QCT system were associated with all types of fragility fractures [63].

MRI

MRI has advantages in assessing bone quality compared with CT, such as the lack of ionizing radiation and the ability to evaluate aspects of bone physiology beyond structure, such as content, diffusion and perfusion of marrow. Its known disadvantages include the cost and complexity of the MRI equipment and analyses. *In vivo* MRI of trabecular architecture is usually performed at the distal radius or calcaneus as these areas are accessible to small high-resolution coils. Nearly all MRI derived structural parameters of the distal radius are better than DXA at differentiating women with and without vertebral fracture [64]. High-resolution MRI of the central skeleton is limited by resolution issues. The resolution of the MRI images limits the application of 3D structural analysis in the hip. The potential of MRI as a means of imaging proximal femur structure, requires improvements in technique and resolution enhancements [65].

Quantitative ultrasound

Quantitative ultrasound is yet another method to measure characteristics of bone strength and density. Several large prospective studies have shown that calcaneal quantitative ultrasound can predict future fracture risk nearly as well as

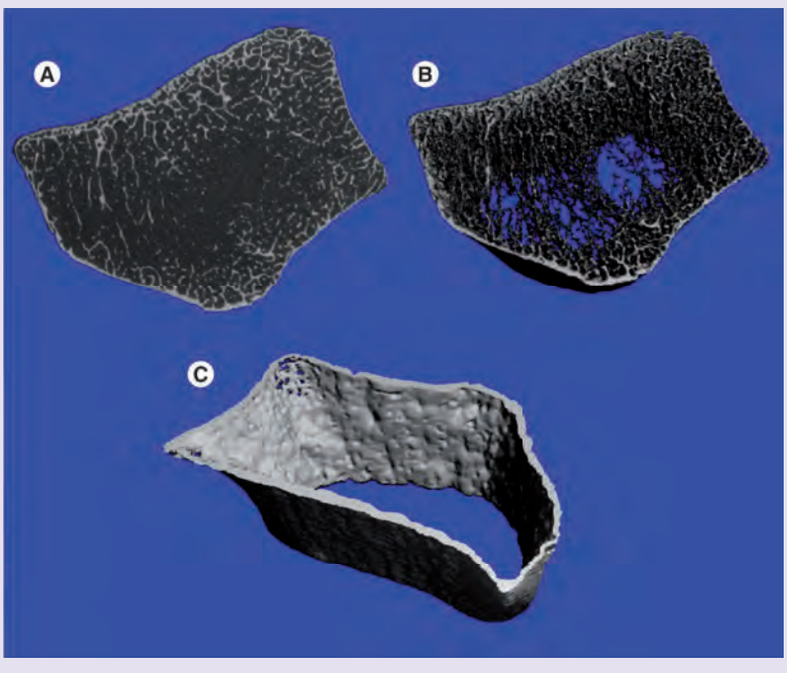

Figure 2. High-resolution peripheral quantitative computer tomography images of the distal radius. (A) 2D image. **(B)** 3D image. **(C)** 3D image of computer-assisted dissected cortical bone.
Produced at the Maastricht University Medical Center.

DXA [66–68]. Unlike DXA, quantitative ultrasound may be able to assess bone quality in addition to BMD [69,70].

Clinical risk factors for fracture

Fracture risk assessment tool

The fracture risk assessment tool (FRAX) case finding algorithm has been developed to predict the 10-year risk of major osteoporotic fractures (e.g., clinical vertebral, wrist and humerus) and hip fractures. Based on a systematic evaluation of major clinical risk factors (e.g., age, personal and family history of clinical fractures, life style, diseases and medications). It can be calculated with or without BMD (**Box 1**) [102]. Using FRAX, diagnostic and therapeutic decisions can be based on absolute fracture risk thresholds, which are available in recently upgraded osteoporosis guidelines in the UK and US [71,72,102]. However, FRAX has several limitations. FRAX does not include fall risks, the clustering of fractures in time (i.e., the risk of subsequent fracture is highest within the first years after a fracture) [6,7,9,73] and the dose of some risk factors, such as the daily and cumulative dose of glucocorticoids or the previous fracture load in terms of number and severity of previous vertebral and nonvertebral fractures [103]. Therefore, FRAX may underestimate fracture risk in individuals with high additional risk exposure, such as recent fracture, recent falls and high dose glucocorticoids.

The Garvan Fracture Risk Calculator

Each year, approximately a third of community-dwellers older than 65 years and nearly one-half of institutionalized persons or persons over the age of 80 years will sustain a fall. Half of them will experience another fall within the next year. Approximately 10–15% of falls result in a fracture, and this is even higher among nursing home residents [74].

The association between fall risks and the risk of fracture has been extensively documented, independent of other risk factors for fractures and of BMD. These fall risks include slowed gait speed, tandem walk and poor vision, postural instability and/or quadriceps weakness and a history of falls, self-reported health self-reported physical activity, impaired cognition, slower walking speed, Parkinson's disease, use of psychotropic drugs with CNS effects and intake of multiple medications [75–78].

The Garvan Fracture Risk Calculator (GFRC) is another tool that is available online to calculate the risk of osteoporotic and hip fracture [101]. The GFRC differs from FRAX, taking into account a history of recent falls (1, 2 and >2 recent falls) and the number of previous fractures (1,2, and >2), but does not include other risks included in FRAX. It also predicts more types of fractures than FRAX. As a result, calculations of 10-year fracture risk differ between the two algorithms. Compared with GFRC, FRAX underestimates fracture risk in patients with two or more fractures and with one or more recent falls. On the other hand, the GFRC underestimates fracture risk in women with a parent history of hip fracture and in women with secondary osteoporosis, compared with FRAX [79]. In spite of these differences, both approaches were reasonably accurate in women [77].

Other fracture risk assessment tools

The MaasFran Fracture Risk Calculator includes the recentness of previous fracture, which increases the risk of subsequent fracture at short term [80]. In patients with a recent fracture, the calculated 10-year fracture risk is higher when using MaasFran than FRAX [80]. Fracture risk calculation using MaasFran is possible using a nomogram [80].

The fracture risk with use of bone glucocorticoids (FIGS) fracture risk calculator includes the daily and cumulative dose of glucocorticoids as a risk factor [81]. In patients on high doses of glucocorticoids, the calculated 10-year fracture fracture risk is higher when using FIGS. However, no FIGS fracture calculator is available for use in daily practice. Most importantly, these tools need prospective validation in other populations.

Future perspective

The etiology of fractures is multifactorial. Low BMD, bone strength parameters, clinical bone and fall-related risk factors all contribute to fracture risk (**Figure 1**). Thus, prediction of fracture risk can be enhanced by combining these predictors, which is possible in daily practice by evaluation of the presence of clinical risk factors, measuring BMD and evaluating the risk of falls.

Calculation of absolute fracture risk by integrating clinical risks, BMD, bone geometry and fall-related risks is attractive, but requires further refinement by integrating these risk factors into a single algorithm for clinical use.

Risk factors assessment is not only valuable for detecting subjects at highest risk for fractures. It will also serve in shared decision making with the patient in order to initiate or not a medical treatment and research on shared decision making is a growing field of interest.

The next challenge will then be to determine at which level of fracture risk, treatment should be initiated. It has been shown in randomized controlled trials that in patients selected on the basis of low BMD or a prevalent vertebral or hip fracture prevention of fractures is possible. Studies will be needed to investigate whether treatment is also effective when patient selection is based on the presence of other risk factors, including structural characteristics of the bone.

Executive summary

- The risk of fractures is multifactorial and depends on material and structural properties of bone and on the intensity, frequency and impact of the trauma.
- Low BMD is a major determinant of bone strength and fracture risk, but most patients with a fracture present with no osteoporosis.
- BMD explains <50% of bone strength and fracture risk.
- Bone strength can be calculated by analysis of 2D and 3D structural images of bone, but this is not yet part of daily clinical practice.
- Fracture risk can be evaluated by integrating BMD with systematic evaluation of clinical risk factors, such as in the fracture risk assessment tool case finding algorithm.
- Previous falls are included in the Garvan Fracture Risk Calculator.
- The dose of glucocorticoids is included in the Fracture Risk in Glucocorticosteroid users.
- The recentness of fractures is included in the Maastricht Fracture Risk Nomogram.
- Further refinement of case finding algorithms will be needed to integrate BMD, bone strength calculations and clinical risk factors into a single algorithm for fracture risk prediction, that can be used in daily practice.

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.	**1**	**2**	**3**	**4**	**5**
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. Your patient is a 53-year-old perimenopausal white female being evaluated for fracture risk. Based on the above review by Dr. Geusens and colleagues, which of the following statements about the effects of bone mineral density (BMD) and bone strength on her fracture risk is most likely correct?

- ☐ **A** Dual-energy x-ray absorptiometry (DXA) is the gold standard for measuring the areal BMD component of fracture risk in daily practice
- ☐ **B** The interpretation of BMD has no known limitations
- ☐ **C** BMD explains >75% of bone strength and fracture risk
- ☐ **D** Bone strength is routinely calculated in clinical practice by analysis of 2D and 3D structural images of bone

2. You decide to use the FRAX case-finding algorithm to determine fracture risk for the patient described in question 1. Based on the above review by Dr. Geusens and colleagues, which of the following is **most likely** included in the FRAX algorithm?

- ☐ **A** Number and timing of previous clinical fractures
- ☐ **B** Family history of clinical fractures
- ☐ **C** Presence, number, and severity of morphometric vertebral fractures
- ☐ **D** Dose of glucocorticoids

3. Based on the above review by Dr. Geusens and colleagues, which of the following statements about clinical algorithms other than FRAX for determining fracture risk is most likely correct?

- ☐ **A** BMD, bone strength calculations, and clinical risk factors are integrated into a single existing algorithm for fracture risk prediction that can be used in daily practice
- ☐ **B** The Garvan fracture risk calculator does not include history of previous falls
- ☐ **C** The fracture risk in glucocorticosteroid users algorithm does not include glucocorticoid dose
- ☐ **D** The Maastricht fracture risk nomogram includes the recentness of fractures