Bone densitometry and true BMD accuracy for predicting fractures: what are the alternatives?

Requirements for clinical densitometric evaluation of fracture risk of an individual patient are obvious: the method must be noninvasive and safe, it should provide adequate assessment of bone fragility, be sensitive and specific enough to detect small differences or changes in structural bone traits that are vital to bone strength, and appreciably add to the predictive ability of prior assessment of fracture risk based on established clinical risk factors of the given patient. At present, clinical evaluation of bone fragility largely rests on dual-energy x-ray absorptiometry (DXA) and the obtained areal bone mineral density (BMD) and the T- and Z-scores derived from it. Whereas BMD correlates strongly with bone strength and low BMD indicates increased relative risk of fragility fractures, the overall proportion of fractures attributable to osteoporosis, as diagnosed by low DXA-measured BMD, remains quite modest. This paradox apparently arises from the limited ability of areal BMD to elicit individual patient's bone strength and from too narrow an insight to multiple factors that truly contribute to fractures. Clinical assessment of patient-specific bone fragility and fracture prediction should rely on comprehensive assessment of individual clinical risk factors accounting for both bone fragility and falling. Regarding the former, it is noteworthy that bone traits derived from 3D bone images have not alone improved the prediction of bone strength compared with BMD, but the combination of independent bone traits seems to do so. This being the case, the biomechanical finite element analysis of 3D bone model holds an excellent promise to yield more meaningful information on individual bone fragility and susceptibility to fractures.

KEYWORDS: BMD ■ bone fragility ■ DXA ■ finite element modeling ■ fracture risk ■ osteoporosis ■ QCT

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Osteoporosis & bone fragility

Every second woman and every fifth man aged 50 years or over sustains a fragility fracture (vertebral, hip, wrist or proximal humerus facture) during the rest of their lifetime [1]. Fractures virtually always lead to temporary morbidity, and with age, the likelihood of permanent and more severe comorbidities markedly increases [2]. For example, of those who sustain a hip fracture, the majority will never reach the same level of physical functioning that they had prior to the fracture; many of those who lived earlier at home will become institutionalized, and one fifth will die during the first year after the fracture [3]. While the present situation readily forms a considerable public health problem, the burden of fragility fractures to our societies is predicted to increase as larger proportions of the population will reach very old and frailty age [4]. Efficient preventive measures to cut this trend are urgently needed.

Cost-effective prevention of any health problem rests on reliable case-finding of individuals who are at high risk to warrant a properly targeted intervention (e.g., preventive lifestyle actions or medical treatment) and those likely to benefit from these measures. The backbone of case-finding is a method that provides a valid (i.e., accurate and clinically meaningful) and consistent (i.e., precise) measurement of the health condition of interest in the given individual. As regards to osteoporosis and related bone fragility, in 1994 the WHO proclaimed the dual-energy x-ray absorptiometry (DXA) the method, and the areal bone mineral density (BMD) the primary measurement of bone status [5]. The operational definition of osteoporosis was set at 2.5 standard deviations (SD) below the young adult mean BMD level expressed as T-score of -2.5 or less.

The diagnostic T-score threshold identifies approximately 30% of the postmenopausal female population as having osteoporosis either at the spine, hip or forearm [6]. Interestingly, the same percentage also equals to the lifetime risk of fractures at those sites [6]. The similarity between these two independent numbers may allure one to conclude that they are synonymous. If so, osteoporosis, as defined by low areal BMD, would be the major underlying factor of fragility fractures and the DXA-measured

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BMD would provide a perfect clinical measurement to assess the probability (i.e., risk) of an individual patient to sustain a fragility fracture. However, there is abundant clinical evidence demonstrating that the areal BMD is not such a measurement, and accordingly, people who sustain a fracture and those who have a low BMD are only partly the same [7–14].

This article elaborates issues that compromise the ability of the present clinical standard, the DXA-measured areal BMD, to predict fractures and outlines future prospects that may facilitate more reliable assessment of bone fragility and fracture risk of an individual patient. Proper evaluation of bone strength, or inversely bone fragility, is an important element to the fracture prediction assessment tool, but not the whole or only element – a much more comprehensive insight to multiple factors that truly contribute to fragility fractures is needed.

Bone fracture: a biomechanical event

Bone stress

Bone fracture is basically a biomechanical event in which the external load imposed on the bone (i.e., applied load or stress) exceeds its structural strength (i.e., ultimate load-carrying capacity or fracture load of the given bone) [15–17]. If the magnitude of applied load and its energy are large enough, even a strong bone can break. However, a weak bone (ie, a truly osteoporotic, structurally deteriorated bone) is much more likely to break than a strong one, but without unexceptional loading, even a fragile bone may survive normal living without fracturing [18–20]. Clearly, a proper assessment of fracture risk prediction requires relevant information on both applied load and bone structural strength. The fracture risk prediction can be formally defined as a simple ratio (Φ) of the applied load to fracture load, termed the factor of risk [21]. When Φ is greater than one, the bone is likely to fail under the imposed load. While simple by definition and interpretation, the clinical implementation of this approach is not necessarily so.

Given the wide spectrum of potential loading events in everyday life, realistic evaluation of the loads on bones is difficult, if not impossible. The loads can vary from frequent low-to-moderate impacts caused by habitual locomotion to rare, but destructively high-impact loads, caused by falls from heights or vehicle collisions. Regarding the practical assessment of individual fracture risk, however, it is reasonable to focus on such loads that can occur while moving/standing on one's feet and falling from the standing height or lifting a heavy object. Simulations based on such stereotypical loading configurations (e.g., one-legged stance, sideways fall onto the greater trochanter, fall on the outstretched hand or lifting an object) in which the bodyweight and height-related forces are applied from biomechanically realistic directions, permit a reasonable approximation of individual loading conditions and thus be of use in the development and application of clinical fracture risk assessment tools.

Bone strength

Bone, as an organ, is a very complex structure, comprising multiple hierarchical levels, that makes the noninvasive evaluation of bone structural strength challenging – even at the coarse level. Bone comprises structural traits from microcracks or resorption lacunae in individual trabecula, via the trabecular microarchitecture and cortical geometry up to the macroanatomy and bulk mineral mass of the whole bone [22]. Each of these traits can contribute separately or interactively to the whole bone strength. In the end, the 3D structure describes the ultimate phenotype of bone and is also the strongest determinant of whole bone strength [23,24]. Regarding the present BMD-based clinical practice, the critical question is to what extent BMD can describe the bone strength of an individual patient and if so, whether BMD is a strong predictor of fragility fractures for the given individual.

As to the prospect of DXA-measured BMD in evaluating whole bone strength, an incisive quote by a distinguished bone biologist John Currey provides a proper orientation to this challenge [17].

"An engineer would laugh if asked to predict the strength (of whatever kind) of a very complex structure like proximal femur, given only the information available to a clinician"

In line with this argument, the error in predicting individual bone strength with BMD can be substantial (i.e., tens of percent) (Figure 1) [25–27], the same the correlation between the areal BMD measured *ex situ* and fracture load can be quite strong – even greater than 0.9 [27–29]. Furthermore, one SD reduction in the DXA-measured BMD (corresponding to approximately a 10–15% lower value or a decrease of T-score by one unit) is associated with approximately doubled relative fracture risk

[30–32]. Also significant, weak correlations have been observed between the increase in BMD in response to drug treatment and the reduction in fracture risk [33,34]. Particularly the high correlation with bone strength and the significant gradient of risk of fragility fractures are given as the strongest arguments for the clinical utility of DXA-measured BMD.

Without depreciating the evident impact of bone fragility on public health, bone fragility, manifest as fractures, concerns primarily an individual patient. Apparently, this issue cannot be properly addressed by correlations observed in various data samples or BMD-associated relative risks obtained from general or specific populations. Instead, an accurate assessment of individual bone strength (or fragility) is what is really needed.

Assessment of fracture risk

DXA-measured BMD

It is well established that low BMD is associated with an increased relative risk of fracture of the given patient, but only at a moderate level [30]. The typical relative risks of approximately two observed in several populations indicate substantial overlap in BMD values between those who have sustained a fracture and those who have not [7–14]. Conversely, this overlap means quite a limited predictive ability for BMD. It should be noted that only relative risks of approximately three or more are considered to be of clinical relevance in individual risk assessment providing areas under of the receiver operating characteristic (area-under-the-curve [AUC]) curve of about 0.8 (one denotes a perfect classification and 0.5 denotes performance that would be obtained just by random guessing) [35]. Given the limited performance of the DXA-measured BMD, one may ask whether the association between incidence of fragility fractures and low BMD (i.e., osteoporosis according to the WHO operational criterion) is strong enough for efficient assessment of individual risk. In essence, relative risks apply to populations and not to individuals.

Using a relevant statistical estimate of population attributable risk (PAR), the overall proportion of fractures attributable to osteoporosis, as defined by diagnostic threshold T-score of -2.5 or less, remained quite modest, ranging only from less than 10 to 44% depending on the type of fracture [8]. For the hip and vertebral fractures, the reported PAR values were 28 and 39%, respectively, based on the total hip and total spine BMD measurements [8]. It has been speculated that even approximately 85% of the rise in age-related fracture risk is not related to BMD [36]. This being the case, there must be several other factors accounting for fragility fractures which are not captured by the DXA-measured areal BMD.

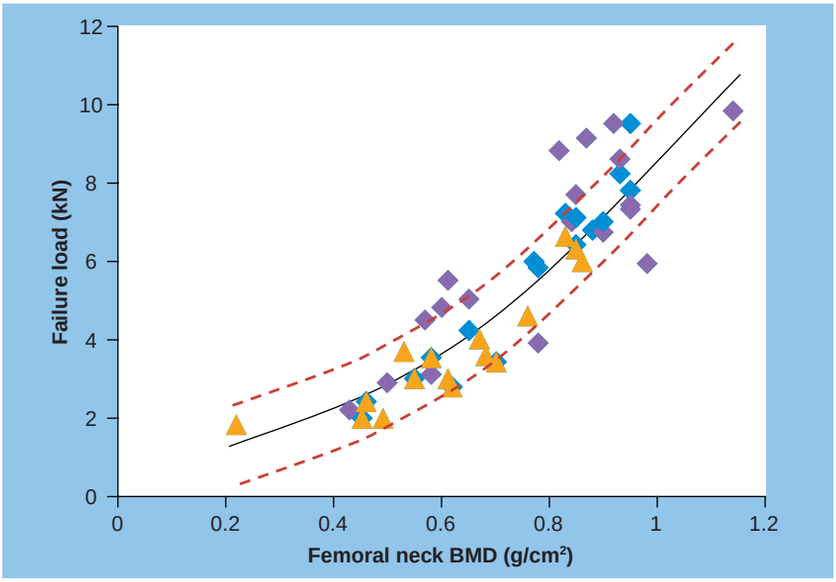

Figure 1. Scatter plot and regression line between femoral neck areal BMD and failure load (F). The data are extracted from three different cadaver studies using the same dual-energy x-ray absorptiometry brand: yellow triangles [25], purple diamonds [26], and blue diamonds [27]. The regression equation obtained from the pooled data is: F (in kN) = 0.845 + 7.456 $BMD^{1.92}$ (r = 0.91), meaning that the areal BMD accounts for 83% of the variability in the femoral neck failure load. Despite the strong correlation, the error in predicting failure load of an individual bone can easily exceed ±1 kN (red dashed lines).
BMD: Bone mineral density.

Bone quality

The substantial overlap between BMD values of fractured and nonfractured patients was well recognized already at the time of operational definition of osteoporosis [7,37], but it took a decade until this limitation of DXA was taken seriously in the osteoporosis community [8–11]. As a potential remedy, the old concept of bone quality dating back to early 1990s [38,39] was revived to fill 'the holes' left by DXA-measured BMD in the assessment of fracture risk [40–43]. Initially, bone quality was attributed to a lumped measure of 3D arrangement of bone tissue in space and its material properties as distinguished from bone quantity represented by bone mass or areal BMD [39]. Later, bone quality was rather loosely defined as the sum of characteristics of the bone that influence the bone's resistance to fracture [43].

Obviously, without a feasible *in vivo* measurement, bone quality remains a fuzzy concept without a tangible link to bone fragility [44]. In

line with the initial definition attributing bone quality not only to the actual 3D description of bone structure but also material bone properties, the concept of bone quality translates directly to the capacity of whole bone to withstand a variety of loading. Unfortunately, bone structural strength cannot be directly measured *in vivo*, the major determinant of bone strength, can be [23,24]. Hence, there remains a need for an *in vivo* methodological solution that could reliably assess the capacity of clinically relevant bones' (e.g., proximal femur, vertebrae, distal radius) to bear loading that may occur as a consequence of falling to the ground (hip and wrist) or lifting heavy objects (spine). If this assessment could be done sufficiently, the limitations in the individual fracture risk assessment arising from moderately performing DXA-measured areal BMD may be overcome, or at least alleviated.

BMD-based risk prediction models

In principle, a reasonable combination of independent strong risk factors could make up an efficient risk prediction tool for fragility fractures and enhance the prediction based solely on DXA-measured BMD [35]. However, many of the commonly used risk factors of fractures are not particularly strong; that is, their relative risks are not greater than three. The pivotal study of Black *et al.* [45] showed that the inclusion of BMD added only slightly to the predictive ability of a model (AUC increased from 0.71 to 0.77) compared with what was already obtained with some clinical risk factors (age, previous fracture, maternal hip fracture, low bodyweight, smoking and use of arms when rising from a chair). Also, meta-analyses of separate clinical risk factors of fragility fractures (previous fracture, family history of fracture, and prior corticosteroid use) have indicated that the inclusion of BMD adds little, if anything, to the predictive ability of the single risk factor alone [46–48]. It is noted, however, that many risk factors are more or less associated with BMD, which can confound the mutual contributions of these factors to fracture prediction. The influence of age, in particular, can be substantial [32,46–48].

At present, the strongest evidence about prediction of osteoporotic fractures comes from the recent meta-analysis of several population-based studies by Kanis *et al.* [49], which demonstrated that while BMD hardly contributed to the predictive ability for nonhip fractures (AUC increased from 0.60 to 0.62 in the validation cohort) compared with that already obtained by established clinical risk factors (body mass index, family history of fractures, use of systemic glucocorticoids, prior fracture, smoking, alcohol intake and rheumatoid arthritis), the inclusion of BMD significantly improved the predictive ability for hip fractures (AUC increased from 0.66 to 0.74 in the validation cohort) over that based on clinical risk factors only.

Quite understandably, both the recent WHO-recommended fracture risk assessment tool, FRAX®, [50,51,201] and other recent fracture risk algorithms [52–57] rely on BMD measurements. While BMD is not necessarily needed for all of these tools, FRAX included, BMD, if available and entered into the model, can substantially modulate the individual risk estimates. In fact, it was recently found that once the femoral neck BMD and age are known, the eight additional risk factors in FRAX do not significantly improve the prediction of vertebral fractures [58].

Altogether, the somewhat inconsistent contributions of BMD and other clinical risk factors observed in different populations underline not only the general challenges of fracture prediction but also those regarding the utility of BMD in the fracture risk assessment of an individual patient. Apparently, dedicated predictive models for each major fragility fracture may need to be developed given the different mechanisms and risk factors of those fractures. That being said, only the strong independent risk factors should be employed. In this context, it is noted that unlike the seminal algorithm by Black *et al.* [45], the other BMD-based algorithms tend to ignore the evident influence of functional ability, or functional limitations and disability of an individual, on the fracture risk [59]. This is surprising, since appropriate information on functional ability can be obtained even in general practice without expensive equipment, [60–62] or in its simplest form, just by asking the patient about his/her impaired imbalance as suggested recently by Wagner *et al.* [63]. Obviously, impaired balance increases the susceptibility to falling and thus underlies many fractures.

Falling

While there is general decline in physical functioning of the population with age [64], it is important to recognize that the between-individual variation can be large exposing some individuals to particularly increased susceptibility to falling and considerable fracture risk.

These high-risk people are the very persons that should be identified in time. Apparently, the inclusion of previous fractures as one predictor in the fracture risk assessment algorithm reflects to some extent a person's tendency to fall, but retrospectively. It would be much efficient to capture this relevant information in advance by assessing a person's physical functioning, and depending on the results then contemplate timely preventive actions (e.g., balance and strength training, and vitamin D supplementation) against falling and fall-related fractures [65]. This is of utmost importance since falling causes more than 90% of hip and wrist fractures and is also involved in 30–50% of vertebral fractures [66–70].

Since the fall-induced load on bone is basically the root cause of bone fracture, quite logically, falling is a strong risk factor of fragility fractures. The relative risk of hip fracture for a sideways fall varies from three to five, while the relative risk of hip fracture can rise to up to 30 as a consequence of direct fall-induced impact on the greater trochanter [66,68,71]. Notwithstanding the fact that only approximately 5% of falls result in fractures, falling is so frequent among the aging population [72,73] that the total number of potentially hazardous events becomes inevitably large. Thus, the role of falling as a major risk factor of most fragility fractures should be appreciated, whereas the predominance of BMD (i.e., DXA-measured osteoporosis) as the major contributor to the incidence of fractures needs reconsideration [74]. In support of this argument, low BMD was recently found less predictive for future limb fractures than reported falls in a large multicenter study [75]. Needless to say that both bone strength and falling (i.e., bone load) are relevant factors to be included in efficient clinical fracture prediction tools.

Assessment of bone strength *in vivo*

DXA-measured BMD

While the DXA-measured areal BMD correlates strongly (correlation coefficient [r] even greater than 0.9) with actual bone strength in *ex situ* biomechanical tests of whole bones (e.g., proximal femur and lumbar vertebrae), it fails to be a reliable descriptor of bone strength of an individual patient (Figure 1). Obviously this failure must account for the fact that many people with normal BMD sustain fragility fractures while some with low BMD (i.e., osteoporosis) do not [7–14]. There are several technical, methodological and biomechanical issues that account for the limited performance of DXA. Understanding of these issues is essential for proper interpretation of BMD results.

The DXA assessment of BMD is based on the measurement of attenuation of low- and high-energy x-ray beams traversing through the body region of interest. It is a physical fact that high-density tissue (i.e., bone) attenuates more x-ray photons than low-density tissues (i.e., muscle, adipose tissue and bone marrow) at given x-ray energy, and the relative difference in the x-ray attenuation declines with increasing x-ray energy. Assuming that the scanned body volume comprises only two absorptiometrically disparate components, bone and homogeneous soft tissue, the areal BMD can be determined from the obtained attenuation data of two disparate x-ray energies – two unknown variables (areal BMD and areal density of soft tissue) and two independent attenuation equations. Accordingly, the measured BMD can be solved accurately if, and only if, the two-component assumption is not violated. Obviously, in real world the patient anatomy does not comply with this assumption. The actual region of interest (ROI) encompasses always both bone tissue and a mixture of soft tissues (muscle and adipose tissues and bone marrow) with varying

Table 1. Correlation (r) between DXA-measured lumbar or femoral neck BMD *in situ* (soft tissues intact) and *ex situ* (soft tissues removed) and the failure load of given bone site.

Bone site	*In situ*	*Ex situ*	Ref.
Lumbar spine			
	0.53		[76]
	0.45–0.48	0.51–0.71	[77]
	0.73	0.69–0.83	[78]
	0.71		[79]
Femoral neck			
	0.63 – 0.78		[79]
		0.84	[27]
		0.96	[26]
		0.82–0.84	[80]
		0.92	[28]
		0.89	[25]
		0.74	[81]
		0.71	[82]
		0.63	[83]
		0.80	[84]
		0.84	[29]
		0.80	[85]
		0.77	[86]

thickness, distribution and composition, which results in too many unknowns to be solved with the DXA principle. This unavoidable violation of the two-component assumption is what fundamentally makes DXA inherently inaccurate and at least partly compromises its ability to predict bone strength of an individual patient. This is also evident from several studies which have consistently found at least somewhat lower correlations between site-specific BMD and failure load in *in situ* conditions than in *ex situ* conditions (Table 1) [76–86].

The inaccuracy of DXA in measuring bone mass or density at different skeletal sites was found to be substantial (mean error approximately 5–7%) in several cadaver experiments already around the time of operational definition of osteoporosis [87–90]. The magnitudes and trends of these inaccuracies were systematically exposed in comprehensive experiments, in which bone, soft tissue and bone marrow phantoms with specified tissue-mimicking x-ray attenuation and density properties were used [91,92]. In short, the areal BMD is over/underestimated if the total x-ray attenuation caused by all soft tissues above and below the bone and by bone marrow within the bone is greater/lower than the total attenuation caused by all soft tissues in both sides adjacent to the bone within the given ROI. Depending on the patient-specific bone structure, bone size and shape, and bone marrow and soft tissue properties, the worst-case over/underestimation of an *individual* BMD can be even tens of percent [91–93]. Inaccuracies of this magnitude (15–25%) have also been observed in cadaver experiments [77,89]. Given this evidence, the possibility that such large inaccuracy errors would not concern clinical *in vivo* DXA scans in some individual cases cannot be ruled out.

As there is no practical way of knowing the patient-specific inaccuracy in advance or correcting it afterwards, the meaning and interpretation of the DXA-measured individual BMD is inevitably blurred to an unknown extent. This uncertainty concerns also the T- and Z-scores derived from the given patient's BMD and (population-based) mean BMD and SD. In-line with this, the recent analysis by Blake and Fogelman suggested that the total uncertainty (95% confidence interval) in individual T-score arising from both inaccuracy and precision can be approximately 1 units [94]. This means that a measured T-score of -1.5 may actually reside between -2.5 (osteoporotic BMD) and -0.5 (normal BMD). Then, for a 65-year old, 160 cm tall, 60 kg Finnish woman without other relevant clinical risk factors, the FRAX-based [201] estimate of 10-year risk of major osteoporotic fracture would vary between 3.0 and 6.2% (twofold increase) and that of hip fracture between 0.2 and 2.0% (tenfold increase). Obviously, this high uncertainty in BMD can compromise not only the diagnosis of osteoporosis but also the individual fracture prediction [95].

Besides recognizing the impact of inaccuracy on BMD, it is also important to understand that the areal BMD is what is primarily measured with DXA. Bone mineral content (BMC) at the given bone site is obtained by multiplying the respective BMD by the projection area (AREA), which is determined from the scan (pixel) data using a crude BMD threshold. In physical terms, the bone pixel areal BMD reflects the product of volumetric density of fully mineralized bone (ρ, which is size-independent bone material property with a virtually constant value of 1.85 g/cm^3) and the thickness (x) of bone mineral at the given point, but lacks the information on how the bone mineral is distributed in the depth direction (parallel with the direction of the x-ray beam). By averaging the bone pixel data over the ROI, the conventional BMD analysis loses relevant information on bone structure but reflects a realistically shaped, uniformly thick (i.e., areal BMD = ρx_{mean}; bone thickness) representation (projection) of the given bone (Figure 2). It can be further shown that the areal BMD is proportional to the product of volumetric apparent BMD (i.e., BMC divided by the volume within the periosteal envelope of the given bone) and square root of the cross-sectional area of the given bone section [96]. This means that the measured areal BMD is directly proportional to volumetric apparent BMD and bone diameter – the bigger (smaller) the bone, the higher (lower) the areal BMD at given apparent volumetric bone density; or the higher (lower) the apparent volumetric BMD, the higher (lower) the areal BMD at given bone diameter.

The above described strong dependence of areal BMD on two independent bone traits makes its tangible interpretation difficult. On the other hand, the contribution of both bone volumetric apparent density (i.e., trabecular number, thickness and separation, relative proportion of cortical bone, cortical porosity) and bone cross-sectional area to the DXA-measured BMD gives a rudimentary

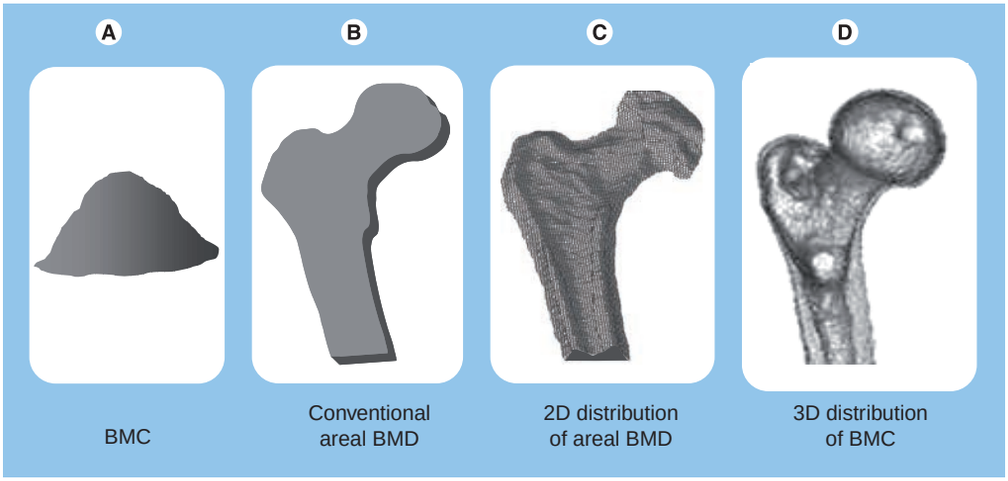

Figure 2. Different representations of bone mineral content. (A) the amount of bone mineral (i.e., building material) without any specific arrangement in space; **(B)** the conventional areal BMD approach denoting a uniformly thick, realistically shaped bone projection, the thickness of which reflects the areal BMD; **(C)** the distribution of areal BMD (i.e., thickness of bone mineral) within the bone projection reflecting some structural information; and **(D)** the realistic 3D distribution of bone mass (i.e., structure) within the actual bone envelope.
BMC: Bone mineral content; BMD: Bone mineral density.

mechanical explanation for why BMD correlates so well with whole bone strength (FIGURE 1 & TABLE 1) [96], and has the proven, although moderate discriminatory and predictive ability in terms of bone fragility [30,32]. The material strength of open-cell (porous) material is associated with the volumetric apparent BMD squared [97]. Apparently, this interpretation applies well to relatively thin-walled bone ends mostly comprising trabecular bone in terms of volume. According to basic mechanics, structural strength (F) against compressive loading is the product of material strength (σ) and the load-bearing area of the given structure (A):

$$F = \sigma A \approx areal\ BMD^2$$

DXA-based bone structure analysis

As discussed above, the raw DXA scan data contain information on the variation of bone mineral thickness (i.e., pixel areal BMD) within the scanned bone projection, which is smoothed down by the conventional BMD analysis (FIGURE 2). Basically this variation can be useful in estimating the structural strength of the given bone [98–101]. The hip structure analysis (HSA) developed by Beck *et al.* is the most common and well-known of these applications [101]. Bone traits such as the cross-sectional moment of inertia (index of flexural rigidity), cross-sectional area occupied by bone mineral (index of compressive strength), bone periosteal diameter, and the distance of the center-of-mass from the bone edge can be calculated for each bone section without any assumptions. In addition, making coarse assumptions on bone cross-sectional geometry and proportion of cortical bone, cortical thickness can be estimated [101]. Furthermore, using this structural information together with axial dimensions and anatomic angles (e.g., neck-shaft angle of the proximal femur) available from the scanned bone projection, different bone strength indices (section modulus Z, index of bending strength; buckling ratio, index of cortical instability) as well as load-induced stresses can be estimated and employed in predicting the bone strength and associated susceptibility to fracture [98–101]. However, it is recalled here that the DXA-based structural analyses are also compromised by the same inherent inaccuracy of DXA method that applies to the areal BMD [91–93].

Consistent with the theoretical biomechanical background, the initial *in vitro* experiments demonstrated that the DXA-based structural analysis provided better correlation (0.89 vs 0.79) with the proximal femur breaking load than the areal BMD [98]. Later, *in vivo* clinical studies showed, however, that these biomechanical approaches could not decisively, if at all, outperform the conventional BMD in the fracture risk assessment [79,102–110]. Apparently, the clearly better *in vivo* precision of BMD measurement compared with DXA-based structural measurements [111,112], and the simple loading configuration (static bending or

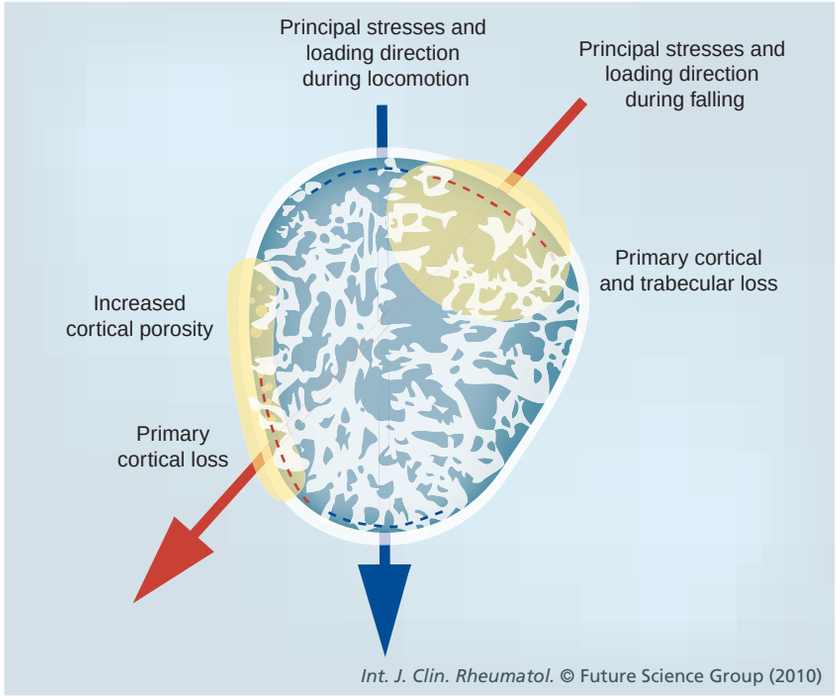

Figure 3. Femoral neck cross-section and the importance of actual bone structure and external loading in the assessment of bone fragility and fracture risk. It is known that structurally deteriorating changes can occur at specific locations of the given bone cross-section (indicated by shaded yellow regions): increased cortical porosity takes place at the anterior wall [115], cortical thinning takes place at the inferoanterior and superoposterior walls [116], and trabecular bone loss takes place at the superoposterior region [117]. Apparently, all these changes account for the cortical instability and overall fragility of the given bone. While these changes may not be crucial in terms of stresses (blue dashed curves) caused by normal locomotive forces (blue wide arrow) but can be so in terms stresses (red dashed curves) caused by fall-induced load (red wide arrow) [118].

compression) applied in the structural analyses explains at least partly the unimproved performance of DXA-based structural analyses in clinical settings.

By contrast to simple load configurations, the actual load that breaks the bone is typically very dynamic in nature (i.e., impact) and may come from a direction that is not properly dealt with mechanical properties derived from the projectional DXA image of the given bone. For example, the proximal femur can be 20–30% weaker in a posterolateral impact caused by a fall compared with direct lateral impact [80,113,114]. Obviously, variation in specific biomechanical factors preceding the fracture can easily overcome the influence of patient-specific BMD on the fracture risk assessment. Instead, adequate information on the 3D bone structure (Figure 2), which is definitely beyond the capacity of DXA, may allow a more realistic analysis of bone structural strength in terms of more appropriate biomechanics (Figure 3) [115–118].

3D bone imaging

At present, the state-of-the-art high-resolution 3D imaging methods can produce quite a detailed *in vivo* description of trabecular architecture and a plethora of different structural descriptors at peripheral bones (e.g., distal radius and tibia) [119–122]. As regards to obtaining specific information on the structure, strength and fracture risk for the clinically relevant lumbar spine and proximal femur regions, quantitative computed tomography (QCT) has been applied to *in vitro* experiments [82,84–86,117,123,124] and *in vivo* clinical studies [125–131]. Besides peripheral applications, MRI has been applied in imaging of the proximal femur both in experimental [81,83,132] and clinical [132–134] studies.

Given the evident potential of present imaging methods to describe bone structure, the ultimate question is what information and how detailed it is required to be for reasonable *in vivo* estimation of bone structural strength in a clinical setting. In principle, such bone traits could include cortical thickness about the bone cross-section, cross-sectional size, shape or dimensions of the bone (i.e., geometry), cortical and trabecular volumetric densities, as well as various descriptors of trabecular structure (trabecular number, spacing and thickness, degree of anisotropy, connectivity indices and fractal dimensions) [125,128,129,132,133]. Obviously, the spatial resolution attainable with *in vivo* imaging limits the accuracy of these structural traits and many of these traits should be considered rather apparent than actual measures [129,133]. It is noteworthy, however, that specific structural traits in themselves have not improved the prediction of bone strength or discrimination/prediction of fractures relative to DXA-measured BMD [81–86,130,131], some findings excluded [123,128]. For example, Mayhew *et al.* in an *in vitro* study observed that the structural analysis essentially improved the discriminatory ability compared with BMD (AUC increased from 0.70 to 0.85) between hip fracture cases and controls [123]. In general, it seems that a combination of independent different bone traits (obtained from multiple regression analysis) provides the best prediction of bone strength [81,82,85,86,124]. These consistent findings imply that instead of analysing separate geometrical or structural bone traits, a more holistic approach, which investigates the bone of interest as a whole and provides an appropriate summary measure of its mechanical competence, might offer a better insight to the relationship between bone

structure, strength and fracture risk. Finite element (FE) modeling is a potential candidate for this purpose. In short, the FE method represents the bone of interest as a mesh of building elements (i.e., blocks, the size and shape of which can vary depending on the application), each of which is specifically located by nodes within the FE model. The 3D bone data (segmented from QCT or MRI scans) are converted, voxel by voxel, to the elements of the FE model that reflects the true 3D geometry and heterogenous density distribution (apparent material properties) of the given bone. It is noted that the resolution (voxel size) of the imaging method, choice or derivation of material properties as well as the loading conditions and constraints affect the accuracy of strength prediction.

Finite element modeling

The FE modeling is a common method in engineering and physics. In bone research, this approach has been successfully employed by *in vitro* biomechanical assessment of bone strength [135–143] and detailed evaluations of stress/strain distributions within loaded bones [144–151] and also in clinical *in vivo* studies [128,152–157] including intervention studies [158,159]. The FE analysis has been applied to all clinically relevant bones susceptible to fragility fractures including proximal femur [135–139,144,145,152,153], vertebrae [140–142,146–148,154,155,158–160], and radius [143,149–151,156,157,161]. In principle, the FE method can integrate the 3D description of bone geometry and structure, and estimated material properties with specific loading conditions and improve the prediction of bone strength as compared with BMD. In the seminal study by Cody *et al.* [136], the FE models explained approximately 20% more of the variance in bone strength than the BMD models. Obviously, the loading conditions of the FE models are deemed to be simple and not represent the actual dynamic loads that bones experience in real life and that eventually may cause the fracture. Nevertheless, since the FE-derived summary measures are based on more realistic 3D description of bone structure and geometry, they may have the asset to outperform the DXA-measured BMD (or any separate bone trait obtained from other imaging modalities) also in *in vivo* clinical assessment of patient-specific bone strength and fracture risk. In a recent large prospective cohort study of older men, the FE-derived load-to-strength ratio was found to be strong risk factor (hazard ratio: 3.1) of incident hip fractures even after adjusting for BMD, age, BMI and study site [153]. Also, in a prospective treatment study of postmenopausal osteoporotic women, the FE results demonstrated a higher standardized response to teriparatide treatment than BMD [159]. In support of these clinical observations, very high correlations (from 0.89 up to 0.98) of FE-derived strength estimates with actual whole bone strength have been observed in several biomechanical studies, [135,136,140–143]. Also, the accuracy of FE predictions has been properly validated with strain gage measurements [137–139].

Apparently, the major benefit of the FE analysis is its ability to provide a more realistic value for the patient-specific factor of risk Φ than can be obtained from DXA or inferred from BMD. Basically this provides the strong rationale for the FE approach in the patient-specific assessment of bone fragility and fracture risk. However, the instrumentation needed for true 3D bone imaging (QCT or MRI) is expensive and under heavy demand for other clinical purposes, which make QCT and MRI less available for specific bone applications. Furthermore, the utility of MRI is compromised by long scan times that are needed for sufficiently high resolution images [132], while the major concern with QCT is the x-ray radiation dose to the patient. Fortunately, modern spiral multidetector QCT systems allow rapid acquisition of true 3D bone images with good (<0.5 mm) spatial resolution at radiation doses comparable to common acceptable radiographic procedures [162]. Besides the need for high-end imaging system, the FE analysis also requires special expertise and software for proper execution, let alone the computational resources needed for segmentation of large amounts of image data and for construction of the 3D bone model and subsequent FE analysis of the model. The more detailed model, the more computational effort and power is needed – up to weeks of supercomputer time [145]. Given the above reasons, it is likely that the FE approach will remain less attractive and be never as extensively used as the present DXA-based BMD and structural approaches. On the other hand, the computing power of present personal computers has tremendously increased during the last decade, appropriate software for segmentation of bone images and FE analysis are yet more accessible, and most importantly, the resolution does not need to be high to develop an appropriate FE model that

can give clinically meaningful results *in vivo* [128,153,154,156–158]. In summary, the FE analysis of the 3D bone model holds an excellent promise for becoming a worthwhile option in the clinical assessment of patient-specific bone fragility and fracture prediction.

Conclusion

No real progress in individual fracture prediction can be achieved as long as the obstinate reliance on DXA-measured BMD continues. Obviously, old methods die hard, but fortunately there is a good prospect that the paradigm shift is about to happen. Appropriate 3D imaging and analysis methods are available, while relevant structural data on different bones from various clinical populations and study settings are accumulating. The rapidly increased interest in DXA-based structural analysis (HSA in particular) since the beginning of this millennium over the conventional BMD can be regarded as a turning point in clinical bone densitometry and represent also the start of broader-scale mechanical thinking in this field [163]. Therefore, the recent evolution and applications of QCT, pQCT, HR-pQCT, MRI and HR-MRI techniques hold much more promise in this respect. Furthermore, these systems permit feasible *in vivo* applications also to clinically relevant proximal femur and lumbar vertebral sites, more sophisticated analyses of cortical and trabecular structural traits, and above all, construction of the 3D bone model and implementation of FE analysis.

Preceded by comprehensive, multiparametric assessment of accessible individual clinical risk factors, the biomechanical approach based on the FE analysis of 3D model of bone to assessing the fracture risk is expected improve identification of high-risk individuals and provide a more reliable estimate of the risk of fragility fractures than that obtained from conventional BMD data or T-scores. A proposed list of factors that may comprise a clinical fracture risk assessment scheme: lifestyle (e.g., exercise habits and smoking), nutrition (e.g., calcium intake, vitamin D and protein), functional ability (e.g., falls, declined muscle power, visual impairment and poor perceived health), body habitus (i.e., frailty and sarcopenia), medications or treatments known to result in bone fragility (e.g., oral corticosteroids) or increase the risk of falling (e.g., psychotropic drugs), conditions or diseases known to increase bone fragility or risk of falling, and bone condition (e.g., previous low energy fractures and shortened stature). It should be noted that many of these risk factors are related to age *per se* and many of them are common to both bone fragility and risk of falling. While the 3D structural assessments or FE analyses have not yet consistently shown essential improvement in the clinical fracture prediction beyond DXA-measured BMD, these approaches rest on solid biomechanical grounds and should thus yield more meaningful information on bone fragility and its susceptibility to fracture, as some pivotal clinical findings have recently suggested [153,159]. More clinical evidence is obviously needed to corroborate the true clinical value of these approaches. In the end, bone fragility and related fractures are a problem of an individual patient, and all novel prognostic approaches should truly facilitate the decision making of practicing doctors and ultimately enhance the clinical outcome of each individual patient.

Future perspective

With the progress of both 3D imaging and computer technologies during the next 5–10 years, it is expected that the present predominance of DXA-measured BMD will gradually decline and both the clinical and scientific focus will be more on 3D imaging of bone structure and subsequent FE analyses of bone strength and rigidity. In support of this, continually accumulating information from FE analyses of 3D bone data of large prospective population studies is expected to show that the comprehensive biomechanical approach represents a real step forward in clinical patient-specific assessment of fracture risk and prediction of fragility fractures. However, given the limited availability of high-end systems and expertise required for 3D imaging and FE analysis, it is obvious that the prudent multiparametric examination of patient-specific clinical risk factors prior to submitting the patient to sophisticated bone imaging and analyses will become a major standard operating procedure and attain much more emphasis in clinical routine than at present.

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Executive summary

Osteoporosis & bone fragility

- Every second woman and every fifth man aged 50 years or more will sustain a fragility fracture (vertebral, hip, wrist or proximal humerus facture) during the rest of their lifetime.
- Most of the fragility fractures occur among patients who are not osteoporotic in the sense of the standard BMD-based definition of osteoporosis (T-score ≤-2.5).

Bone fractures: a biomechanical event

- Bone fracture is basically a biomechanical event which occurs when the external load on bone exceeds its structural strength.
- Fall-induced loads are a common root cause of all types of fragility fractures.

Assessment of fracture risk

- Dual-energy x-ray absorptiometry (DXA)-measured low bone mineral density (BMD) is associated with an increased relative risk of fragility fractures, but only moderately.
- DXA-measured BMD has limited ability to identify individual patients who are truly susceptible to fragility fractures.
- Inclusion of DXA-measured BMD adds only slightly-to-moderately to the predictive ability obtained with clinical risk factors of fragility fractures only.

***Assessment of bone strength* in vivo**

- Error of DXA-measured BMD in predicting bone strength can be tens of percent for an individual patient.
- The 3D bone structure is the major determinant of bone strength and accordingly, adequate structural information permits a more realistic assessment of patient-specific bone fragility than DXA-measured BMD.
- Specific structural traits of bone obtained from 3D bone imaging have not separately improved the prediction of bone strength relative to DXA-measured BMD.
- A more holistic approach involves investigating the bone as a whole mechanical unit and providing an appropriate summary measure of its mechanical competence this provides a better insight to the relationship between bone structure, strength and fracture risk.

Conclusion

- Correct assessment of patient-specific fracture risk requires relevant information both on patient-specific 3D bone structure and geometry as well as on load configuration in typical fracture situations.
- Prudent multiparametric assessment of all established clinical risk factors, also including the evaluation of functional ability and falls, is expected to become the major clinical approach to identifying patients at especially high risk of fragility fractures.
- Biomechanical finite element analysis of 3D bone model holds an excellent promise to yield more meaningful information on individual bone fragility and risk of fracture.

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