Assessment of bone fragility with clinical imaging modalities

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Abstract

Osteoporotic fractures are a vital public health concern and have created a great economic burden to our society. Therefore, early diagnosis of patients with high risk of osteoporotic fractures is essential. The current gold standard for assessment of fracture risk is the measurement of bone mineral density using dual-energy X-ray absorptiometry. However, such techniques are not very effective in the diagnosis of patients with osteopaenia. Doctors are usually unable to make an informed decision regarding the treatment plan of these patients. In addition to bone mineral density, advanced imaging modalities have been explored in recent years to assess bone quality in other contributing factors, such as microarchitecture of trabecular bone, mineralisation, microdamage and bone remodelling rates. Currently, the microarchitecture of trabecular bone can be evaluated in vivo by high-resolution peripheral quantitative computed tomography techniques, which have a resolution of 80 µm. However, such imaging techniques still remain a high-end research tool rather than a diagnostic tool for clinical applications. Thus, the limited accessibility and affordability of high-resolution peripheral quantitative computed tomography have become major concerns for the general public. Alternatively, combining bone mineral density measurements with stochastic assessments of spatial bone mineral density distribution from dual-energy X-ray absorptiometry images may offer an economic and efficient approach to non-invasively evaluate skeletal integrity and identify the at-risk population for osteoporotic fractures. The aim of this critical review is to assess bone fragility with clinical imaging modalities.

Conclusion

High-resolution quantitative computed tomography imaging technique may provide direct measurements of microarchitectures of trabecular bone in vivo. However, it is an expensive method of imaging modality.

Introduction

Osteoporosis is a skeletal disease in which loss of bone mass and deterioration of bone microarchitecture cause a reduction in bone stiffness and strength, thus resulting in an increased risk of fragility fractures⁴. Early diagnosis of patients with high risk of fragility fractures is important due to the elevated rate of morbidity and even mortality, which has made it a vital public health concern and a great economic burden to our society⁵. The current gold standard for diagnosis of osteoporosis and assessment of fracture risk is the bone mineral density (BMD) measured using dual-energy X-ray absorptiometry (DXA).

Although BMD from DXA provides important information about risk of fragility fractures, assessments on BMD alone do not cover the full spectrum of the fracture risk. Numerous studies have indicated that bone strength is only partially explained by BMD⁶. In fact, BMD is a measure of bone mass or quantity of bone. However, bone fragility is not only dependent on its quantity, but also its quality. Bone quality is defined as the totality of features and characteristics that influence a bone’s ability to resist fracture⁷. Such features may include, but may not be limited to, ultrastructure, microarchitecture, microdamage and remodelling rates in bone. Among the features, the microarchitecture of trabecular bone has been recognised as a major contributor to bone fragility.

There are several recently developed approaches that can provide complementary information for assessing fracture risks in addition to BMD. One of them is to develop high-resolution imaging modalities to directly visualise three-dimensional (3D) structure of trabecular bone. The underlying hypothesis is that bone architecture contributes to bone strength. With recent advancement in imaging techniques, high-resolution images using computed tomography (CT) and magnetic resonance imaging (MRI) could be directly used to assess 3D microarchitectures of trabecular bone.

Another approach is to make full use of the existing two-dimensional (2D) projection image modalities and to employ stochastic image-processing techniques to extract useful information on microarchitecture characteristics of bone. In this case, the resolution of the image is no longer essential. The important thing is to recover the information that is indicative of architectural characteristics of bone and can be used to assess the resistance of bone to fracture. To this end, the objective of this article is to review the current progress in using imaging modalities, both 2D projection images and 3D high-resolution images, to assess bone fragility in the clinical settings. The focus of this review article is on 2D imaging modalities since numerous review articles are available for 3D imaging modalities⁸⁻⁹.
Fractal texture analysis analysis of radiographs

Fractal texture analysis, a useful imaging technique, has been successfully applied to high-resolution 2D radiography images (Figure 1) to extract the hidden geometric and microstructural features. Such analyses are based on the concept of fractal geometry. Fractal geometry can be used to define the complex objects that cannot be described by traditional geometric features, such as size and shape. Such objects possess a character of self-similarity, meaning that they can be split into different self-similar pieces at various scales or magnifications while the fractal geometry of these pasts remains similar to that of the whole object. Fractal dimensions are the characteristic dimensions of fractal geometry, with the dimension of a point, a line, a surface, and a volume being defined as 0, 1, 2, and 3, respectively. Different from conventional geometry, the fractal dimension is not an integer but fractional, representing something between the conventional dimensions (e.g. point, plane). Fractal dimension is a measure of how complex the structure of a self-similar object is, which is defined as a ratio of the logarithm of the number of self-similar pieces to the logarithm of the magnification factor. Fractal dimensions can be determined using a box counting algorithm. This measure provides a statistical index of complexity of structure pattern and its changes with varying measuring scales.

In clinical studies, fractal analyses of trabecular bone from calcaneus and distal radius radiographs have helped distinguish the patients with osteoporotic fractures from those in an age-matched control group. For example, the fractal analysis of texture on calcaneus radiographs was able to discriminate osteoporotic patients with vertebral fracture from controls.

Fractal analysis was also applied to radiographs of distal radius and found that fractal dimensions were significantly different between subjects with and without hip fractures. The power of fractal dimension analyses for predicting fracture risks is comparable to BMD for trabecular bones at the distal radius, but lower than that of total hip BMD. In dental settings, fractal analysis of panoramic images has also detected osteoporotic changes in mandibular canine/premolar trabecular bone.

In in vitro studies, fractal analysis of radiographs has been used to predict 3D microarchitecture of trabecular bone. For example, 2D texture analyses of calcaneus and femoral neck from micro-CT images have predicted 3D microarchitecture parameters of the trabecular bones. Another study has examined the high-definition macro-radiography of trabecular bone in human lumbar vertebrae using the fractal analysis and has found that the horizontal and vertical trabecular organisation patterns are different between low- and high-BMD groups. The fractal feature of trabecular bone in knee osteoarthritis is a more sensitive marker of the disease than BMD. Combining BMD values with fractal textural analysis of femoral radiographs from a high-resolution X-ray device has shown significant improvement for predicting the fracture load of human femurs, compared with the results obtained from either of the two measurements alone.

In addition to plain radiographs, texture analysis has also been applied to other imaging modalities. For example, it has been applied to quantitative CT (QCT) of human vertebral bodies and photomicrography of transiliac crest biopsies and has helped distinguish osteoporotic bone structure from normal bone structure. Fractal analysis is also used in high-resolution MRI of distal radius from cadavers. The fractal
analysis provides the information independent of BMD in predicting failure loads of distal radius.

Although texture analysis on high-resolution radiographs has been performed to identify the parameters that are correlated with microarchitectures of trabecular bone, it has rarely been applied to 2D projection images from DXA scans. The reason is largely due to the limited resolution of DXA scans because fractal dimension analysis requires a large projection surface and distinguishable textures from high-resolution images\(^{24}\). These constraints make it unsuitable for analysis of small surface with moderate resolution, such as DXA images.

**Stochastic analysis of 2D projection images**

**Bone heterogeneity and random field**

Although it was still debatable on what spatial resolution is required for clinical assessments of bone fragility, the current consensus is that the image resolution required for clinical evaluations may be much less than that needed in basic research\(^6\). The improvement of imaging resolution would become non-essential if useful information from bone microarchitecture, such as heterogeneity of spatial mineral distribution, can be extracted from the low-resolution images. Theoretical arguments and empirical data have indicated that the heterogeneity of mineral spatial distribution in bone may be used to reflect some features of trabecular architecture that contribute to the resistance of bone to failure\(^{25,26}\). Therefore, there is the clinical significance to assess such spatial heterogeneity in bone. Luckily, variations of grey values in 2D projection images, such as DXA images, actually represent the spatial distribution of bone mineral. In addition, the variation of bone mineral distribution is statistically random as it results from numerous complex biological processes (e.g. mineralisation, bone remodelling) in a highly non-linear and unsystematic fashion.

Thus, we need to adopt stochastic approaches to examine the 2D projection images and quantitatively assess the heterogeneity of spatial mineral distribution.

**Stochastic processes and experimental variograms**

Stochastic parameters can be used to represent spatial variations in BMD through a random field approach characterised by an exponential covariance function. Current techniques for quantifying bone heterogeneity consist of descriptive statistics such as mean and standard deviation. However, these parameters do not describe the spatial variations of bone properties. Stochastic assessment of distribution of BMD in 2D projections images of trabecular bone can be described by experimental variograms, which have been widely used in geosciences\(^{27–29}\).

Previous studies have introduced experimental variograms to describe the inhomogeneity of bone properties\(^{24,30,31}\). To determine experimental variograms, a semi-variance, \(\gamma(h)\), needs to be defined first as the half of the expected squared differences of BMD between any two locations with a lag distance of \(h\).

\[
\gamma(h) = \frac{1}{2m(h)} \sum_{i=1}^{m(h)} \big[ E[(Z(x_i) - Z(x_i + h))^2] \big] 
\]

(1)

where \(m(h)\) is the number of data pairs for observations with a lag distance of \(h\). A typical experimental variogram of DXA images at the hip region (Figure 2) indicated that semi-variance of BMD in DXA images increased with increasing lag distance and reached a plateau, also known as the sill of variograms. It is suggested that as the lag distance increased, the local BMD became more dissimilar on average. This is consistent with the description of a random field in that values at widely separated places are less similar.

Moreover, mathematical (authorised) models are needed to quantitatively describe the mineral distribution in bone using experimental variograms. Examples of simple authorised models are exponential, Gaussian and spherical models. Among them, exponential model

\[
\gamma(h) = c_2 - c_1 \exp\left(\frac{-h}{\lambda}\right)
\]

\(\lambda = 35.8\) mm; \(c_2 = 11.2, c_1 = 1132\)

(2)

Figure 2: Stochastic assessment of bone mineral density distribution from DXA scans of hip. (a) DXA images; (b) variogram and exponential model to fit the experimental variogram.

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Stochastic measures of 2D projection images of trabecular bone

Assessments using stochastic analyses of 2D projection images are significantly correlated to the microarchitecture and mechanical properties of trabecular bone\(^\text{23}\). Using a set of experimental data (micro-CT images and mechanical properties) of 15 cylindrical trabecular bone specimens from six male human cadavers (48 ± 14 years old)\(^\text{34-37}\), a recent study was performed to verify the correlation of the stochastic assessments based on 2D projection images with the real microarchitecture and mechanical properties of the specimens. In this study, 2D projection images of trabecular bone were generated from high-resolution micro-CT scans by averaging the areal grey values of all scans. Stochastic assessments were performed on the 2D projection images through the aforementioned stochastic analysis. The specimens were divided into two groups with distinct bone porosities (Figure 4a, d). The corresponding 2D projection images exhibited a smoother variation of BMD distribution for the high-porosity group, whereas a smaller correlation length implies a smooth variation, whereas the control group (\(N = 8\)) consisted of age-matched subjects without osteoporotic fractures. The stochastic parameters (i.e. correlation length, sill variance and nugget variance) were estimated from the distribution of BMD in the total hip region (Figure 2).

Logical regression models were used to estimate the combined power by both BMD and stochastic parameters in predicting the risk of hip fractures. The outcome of logical regression is represented by a receiver-operator curve (ROC; Figure 3). The area under the ROC (AUC) indicates the accuracy of the logical regression model, with AUC = 1 representing a perfect prediction, whereas AUC = 0.5 representing a worthless test. The analyses indicate that none of the measurement alone has a statistically significant power in predicting bone fracture risks (Table 3). However, the combined power with both BMD and stochastic parameters is statistically significant (\(p < 0.05\)) in predicting bone fractures, showing AUC = 0.792 with confidence intervals between 0.562 and 1.000 (Table 1, Figure 3).

| Table 1. The AUC for logistical regression models. |
|-----------------|---------|--------|--------|
| Model            | AUC     | SE     | p-value |
| BMD              | 0.553   | 0.146  | 0.7     |
| Correlation length | 0.736   | 0.131  | 0.102   |
| Nugget variance  | 0.653   | 0.137  | 0.29    |
| BMD + correlation length + nugget variance | 0.792   | 0.117  | 0.043   |

AUC, area under the receiver-operator curve; BMD, bone mineral density; SE, standard error.

| Table 2. Regression analyses of combination of BMD and sill variance from high resolution 2D projection images (50 µm). |
|-----------------|---------|--------|--------|
| Model            | R\(^2\)  | Adjusted R\(^2\) | p-value |
| Strength ~ BMD   | 0.63    | 0.61   | <0.001 |
| Strength ~ BMD + sill variance | 0.83    | 0.80   | <0.001 |

BMD, bone mineral density; 2D, two-dimensional.

Figure 3: The ROC curve for a combination of BMD and stochastic parameters.

in predicting hip fractures for patients with osteopenia whose T-scores are between −1.0 and −2.5 (ref. 32). DXA scans of the total hip region obtained from 17 post-menopausal women with osteopaenia were analysed. The fracture group (\(N = 9\)) included subjects with a history of hip fractures, whereas the control group (\(N = 8\)) consisted of age-matched subjects without osteoporotic fractures. The stochastic parameters (i.e. correlation length, sill variance and nugget variance) were estimated from the distribution of BMD in the total hip region (Figure 2).

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Critical review

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Critical review

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(Figure 4): Quantification of spatial distribution of bone mineral density in 2D projection images. (a) a slice of microCT images with a low bone volume fraction (BV/TV) = 0.13; (b) 2D projection image of the specimen with low bone volume fraction; (c) the variogram of the trabecular bone specimen with low bone volume fraction; (d) a slice of microCT images of a dense specimen with BV/TV = 0.33; (e) 2D projection image of the dense specimen; (f) the variogram of the dense specimen.

(Figure 5): Sill variance of bone mineral density distribution had significantly positive relationships with (a) elastic modulus ($R^2 = 0.81$, $p < 0.001$), and (b) ultimate strength ($R^2 = 0.82$, $p < 0.001$).

group (Figure 4b) and a more acute variation of BMD distribution for the low-porosity group (Figure 4e). The semi-variance in the variogram of trabecular bone with a high porosity or low bone volume fraction (BV/TV $= 0.13$) reached the plateau slowly at a low sill variance (Figure 4c; $c = 1928$) whereas the other one (BV/TV $= 0.33$) arrived at the plateau relatively rapidly at a higher sill variance (Figure 2f; $c = 4097$). Significant positive relationships were observed between sill variance and the elastic modulus (Figure 5a, $R^2 = 0.81$, $p < 0.001$) and between sill variance and ultimate strength (Figure 5b, $R^2 = 0.82$, $p < 0.001$). Additionally, the
sill variance of BMD distribution in bone was correlated with microarchitecture parameters. Linear regression analyses indicated a significant positive relationship between sill variance and bone volume fraction (Figure 6a, $R^2 = 0.56$, $p = 0.001$). Similar relationships were also observed between the sill variance of BMD distribution and other microarchitecture parameters, i.e. bone surface-to-volume ratio (Figure 6b, $R^2 = 0.54$, $p = 0.002$), trabecular thickness (Figure 6c, $R^2 = 0.54$, $p = 0.002$), trabecular number (Figure 6d, $R^2 = 0.48$, $p = 0.004$), trabecular separation (Figure 6e, $R^2 = 0.50$, $p = 0.003$), and anisotropy (Figure 6f, $R^2 = 0.37$, $p = 0.02$).

Moreover, combining BMD with the sill variance (Table 2) derived from 2D projection images ($R^2 = 0.83$) provided a better prediction of bone strength than BMD alone ($R^2 = 0.63$). Thus, it is promising to extend the stochastic assessment of 2D projection images to routine DXA scans, thus offering an improved methodology to predict bone fragility with marked clinical significance.

Figure 6: Sill variance of distribution of bone mineral density had significantly positive relationships with microarchitecture parameters (a) bone volume fraction; (b) bone surface-to-volume ratio; (c) trabecular thickness; (d) trabecular number; (e) trabecular separation; and (f) anisotropy.
specially designed coils in the newest high magnetic field clinical scanners. Such in vivo imaging technique can achieve an in-plane resolution of 150 µm and a slice of thickness of 250 µm. The apparent trabecular properties obtained from the MRI technique have shown strong correlations with measurements of trabecular microarchitecture from high-resolution techniques such as HR-pQCT. Some have reported that the patients with hip and vertebral fractures can be distinguished from control subjects using MRI-derived parameters. Future developments need to address the current limitations of high-resolution MRI, such as the requirement for specialised coils, the limitation to assessment at peripheral sites, and the relatively long acquisition times.

One of the most promising 3D imaging techniques is HR-pQCT (i.e. in vivo micro-CT technique). The effectiveness of assessing trabecular microstructures of tibia and distal radius with HR-pQCT has been demonstrated in a number of recent studies in clinical settings. For example, deterioration of microstructure of distal radius and tibia has been observed in women during and after prolonged bed rest. Differences in bone microarchitecture are detected between post-menopausal Chinese-American and white women. By examining the distal radius and tibia in daughter–mother pairs using HR-pQCT, it has been demonstrated that trabecular bone in childhood can be used to predict both trabecular and cortical morphology in adulthood. In addition, HR-pQCT has also been used to monitor the usefulness of countermeasures of bone loss such as exercise and nutrition, whole-body vibration, and oral ibandronate.

Furthermore, in vitro studies have also verified the effectiveness of HR-pQCT in assessing bone microstructures. Comparison of bone microarchitecture of femoral necks evaluated by HR-pQCT and conventional histomorphometry has demonstrated that significant correlations were found between both techniques for trabecular bone volume, trabecular number, trabecular thickness, trabecular separation and trabecular connectivity. Individual trabecular segmentation-based morphological analysis has been applied to both HR-pQCT images and micro-CT images of human tibias and indicated that individual trabecular segmentation measurements of HR-pQCT images are highly reflective of the trabecular bone microarchitecture.

The major limitations to the HR-pQCT technique are that it needs specialised equipment, is restricted to evaluation at appendicular sites and employs ionising radiation, which may limit its use in certain patient populations.

**Conclusion**

HR-pQCT imaging technique may provide direct measurements of microarchitectures of trabecular bone in vivo. However, we have limited access to such facilities and the affordability is a major concern for the general public. Such an imaging modality may remain a high-end research tool to help understand bone fragility. On the other hand, the combination of BMD and stochastic assessment of distribution of BMD may offer an economic and effective approach to non-invasively evaluate skeletal integrity and identify the at-risk population for osteoporotic fractures.

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Abbreviations list
AUC, area under the ROC; BMD, bone mineral density; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; HR-pQCT, high-resolution peripheral QCT; MRI, magnetic resonance imaging; QCT, quantitative CT; ROC, receiver-operator curve; 2D, two-dimensional; 3D, three-dimensional.

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