

3D Imaging Bone Quality: Bench to Bedside

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Abstract

Introduction

Measuring the health of bone is important for understanding the pathogenesis, progression, diagnosis and treatment outcomes for fragility. At present the most common method for measuring bone health in a clinical setting is to assess skeletal mass. The current gold standard is dual-energy X-ray absorptiometry (DXA) which models bones as 2D objects and measures areal bone mineral density (BMD). However, BMD only accounts for 50% of bone strength and the technique ignores other important factors such as cortical geometry and trabecular architecture, which are also significant contributors. Consequently a new concept of 'bone quality' has developed the material and structural basis of bone strength and fragility. As yet though, a suitable non-invasive method has not been developed for measuring quality in living patients. The aim of this paper is to discuss how bone quality might be visualised, quantified and applied in a clinical setting.

Discussion

The most useful imaging techniques are likely to be clinical-CT and MRI. Both modalities have been used successfully to characterise bone macro-structure in 3D e.g. volume fraction and orientation. More recently *in vivo* systems with high

resolution (~0.100–0.200 mm) have been developed that can capture some aspects of bone micro-architecture. Alternatively 3D models created using clinical-CT and MRI can be used to virtually simulate loading on a computer and calculate bone mechanical properties. Analysed together these morphological and mechanical data sets might allow clinicians to provide screening programmes for osteoporosis and calculate individual fracture risk. Especially if applied as part of a holistic approach utilising patient meta-data on risk factors for metabolic bone disease (e.g. FRAX). As well as improve primary and secondary care by setting treat to target criteria for pharmacological therapies and planning surgical interventions or following up treatment outcomes.

Conclusion

In the short to mid term the expense of 3D imaging and (in the case of CT) the risks associated with ionising radiation are going to restrict image resolution. Therefore, in order to achieve the goal of bringing bone quality from bench to bedside, future research needs to be directed towards better analysis of 3D bone geometry at sub-optimal resolution.

Introduction

Bone Quality

Research into bone fragility is impeded because there is no accurate, precise and inexpensive method for measuring bone strength—the ability to resist fracture¹. For many years the most widely used technique for estimating bone strength has been densitometry, which measures bone mineral density (BMD). A variety of imaging techniques have been employed to measure BMD including

dual-energy X-ray absorptiometry or DXA², ultrasound³ and peripheral computed-tomography or pQCT⁴. Originally it was thought that bone strength was almost entirely explained by density⁵. However clinical observations did not support the data, pharmaceutical trials revealed that anti-resorptive therapies (such as bisphosphonates) reduced fractures to a greater degree than predicted from increases in BMD: see⁶ and references therein. This was because densitometry failed to take into account the importance of cortical geometry and trabecular architecture for bone strength. Many research articles have since shown that BMD accounts for only about 40–50%⁷ of the *in vitro* compressive strength of a bone whilst structure can account for as much as 30–40%⁸. Following these discoveries, the material (i.e. density) and structural (i.e. non-density) factors were combined into a new understanding of bone strength—termed bone quality, operationally defined as the structural and mechanical basis of bone strength^{1,9}. Quality is an amalgamation of all the factors that determine how well the skeleton can resist fracturing, such as micro-architecture, accumulated microscopic damage, the quality of collagen, the size of mineral crystals and the rate of bone turnover¹⁰.

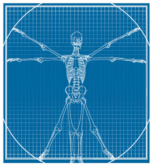
Aims and objectives

Although the concept of bone quality provides a framework for summarising and explaining the determinants of bone strength a metric, method or protocol for measuring bone quality has been elusive. At present there are no satisfactory clinical means to assess bone quality. Such a protocol would be very useful for screening, monitoring and treating

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bone fragility. Therefore, the aim of this paper is to discuss how bone quality might be visualised, quantified and applied in a clinical setting.

Discussion

Imaging bone quality non-invasively

Non-invasive 3D imaging techniques can provide structural information about bone, beyond simple densitometry¹¹. The obvious candidates for non-invasive imaging of bone quality are CT¹²⁻¹³ and MRI¹⁴. CT is a radiographic imaging technique that maps tissue density distribution, as measured by X-ray transmission (Figure 1). MRI uses magnetic fields and radio waves to produce an image that is dependent on the distribution of hydrogen in the body. Each modality creates a 3D computerised model made of voxels (the three-dimensional equivalent of a pixel), each assigned a grey value based on the tissues represented within.

The main factor limiting the usefulness of CT and MRI is spatial resolu-

tion—i.e. the ability to resolve two objects of similar density/hydrogen content respectively that are situated close to one another. Resolution is largely determined by the size of the voxels (Figure 2). Typically the resolution of a 3D scan is between 2 to 5 times greater than the voxel size¹⁵. *In vivo* CT scanners produce scans with smaller voxels than MRI and therefore have the potential to create higher resolution images of bone structure. However, the resolution of CT scans is also dependent upon the energy of the X-ray beam and is therefore limited by dose (Figure 1).

The most common *in vivo* CT systems are volumetric scanners (vQCT) such as the whole body scanners typically found in hospitals. The smallest voxels are usually around 0.3×0.3×1.0 mm (pixel length × width × slice). Hence the systems can be used to visualise cortical geometry and trabecular density distribution at the macro-scopic level. Individual trabeculae cannot be visualised because the elements (<0.250 mm)

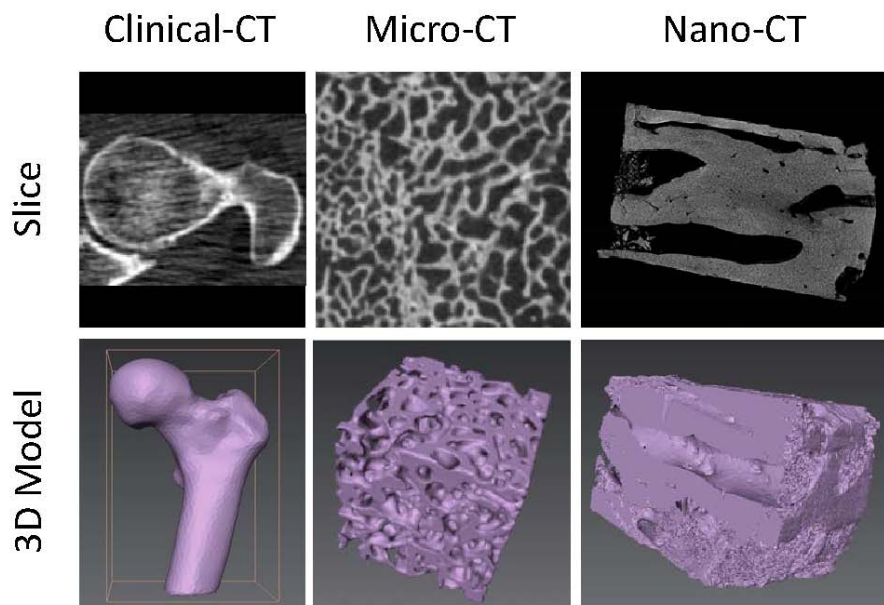


Figure 1: Computed tomographic imaging modalities. Clinical-CT scanners use lower radiation levels and can scan whole bodies but the resolution is too low to visualise tissue level structures. Micro- and nano-CT can image individual trabeculae and even micro-cracks respectively, but the radiation is too high for *in vivo* scanning.

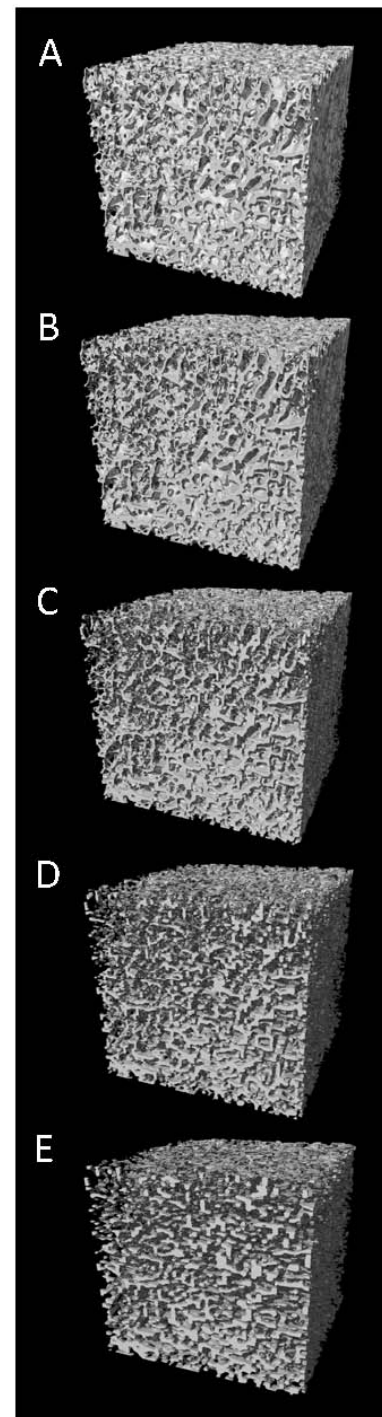
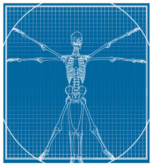


Figure 2: The effect of voxel size the accuracy of 3D models. With increasing voxel the spatial resolution of a scan decreases. From (A) 0.050 to (B) 0.100 mm the 3D structure can be clearly visualised. At (C) 0.200 mm the larger voxels start to miss some features (compare top left hand corners of models). Above (D) 0.300 and (E) 0.400 mm the architecture deteriorates.

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disappear inside the voxels. A phenomenon referred to as partial volume averaging which results from materials of different density occupying a single voxel and thus being represented by an averaged grey value (Figure 3). More recently though high-resolution (*hrCT*) systems have been developed than can produce voxels that are $0.090 \times 0.090 \times 0.200$ mm (e.g. XtremeCT, Scanco, Switzerland). The systems can image trabecular micro-architecture but the trade off is reduced field of view so *hrCT* systems are generally restricted to imaging only the periphery of the body such as wrists and ankles.

Likewise hospital MRI scanners typically scan voxels approximately 0.500^3 mm, but high-resolution (*hrMRI*) systems that can achieve 0.100^3 to 0.200^3 mm are in development^{16–18}. Unlike clinical-CT systems (which are limited by the energy and therefore the path length of the x-rays) the *hrMRI* systems are not restricted to peripheral regions of the body. MRI is not ideally suited to imaging bone though because scanners map the distribution of water on the body and hard tissues have a relatively low water content (Figure 4). Consequently the MRI signal for trabecular bone itself is not visualised as such and trabeculae appear as a signal void surrounded by high-intensity fatty bone marrow¹⁹. It is possible to visualise the bone more clearly by simply inverting the image grey scale.

Quantifying bone quality non-invasively

Currently the key to measuring bone strength *in vivo* using either CT or MRI is to get a handle on the meaning of the voxel grey values. This has been attempted in two ways. The distribution of grey values has been used to quantify the macro- and even some aspects of microstructure that are correlated with mechanical properties²⁰. An alternative approach has been to measure mechanical properties

more directly by using 3D image data to create computer models for 'virtual' mechanical testing²¹. Experimental mechanical testing can be used to validate computer-modelled measure of mechanical properties (Figure 5)

Baum and colleagues^{22–23} attempted to estimate the mechanical strength of bone using low-res *in vivo* CT and MRI scans of the proximal femur and distal radius respectively. Cadaveric femora were clinical-CT scanned at $0.190 \times 0.190 \times 0.500$ mm voxel size, whilst the radii were *hrMRI* imaged at $0.156 \times 0.156 \times 0.300$ mm. Hence the in plane pixel size was small enough to

visualise the largest trabeculae but resolution was ultimately limited by the slice thickness. In both studies trabecular macro-structure was characterised by measuring bone [volume] fraction in 3D. Microstructure was analysed in 2D by applying traditional histomorphometric techniques such as the medial intercept length method to calculate trabecular thickness, number and separation²⁴. Given the large size of the voxels in comparison to individual trabeculae the measurements are usually referred to as 'apparent' because the scans cannot actually resolve the

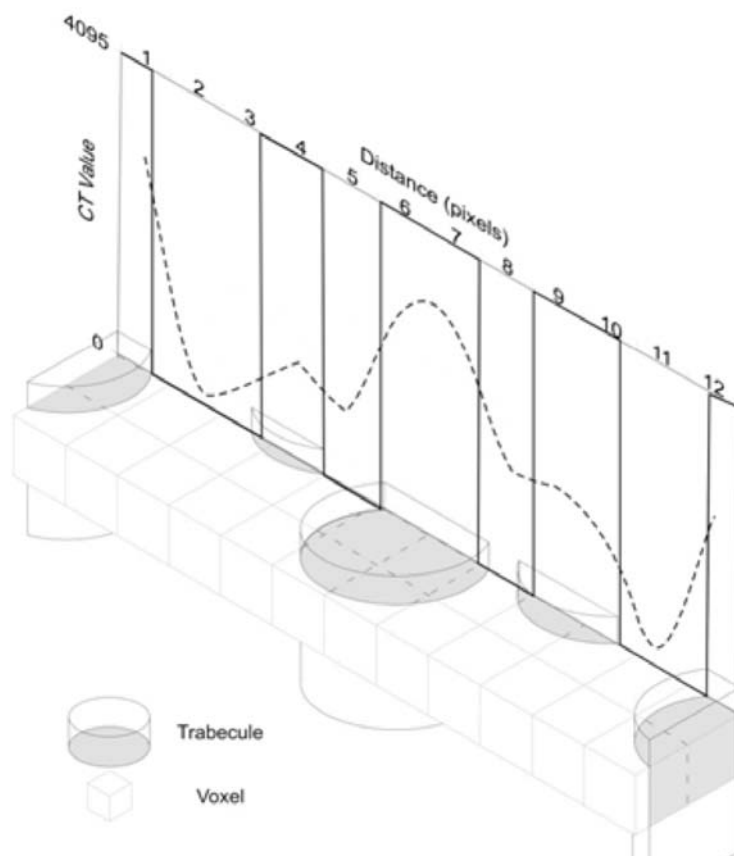


Figure 3: Partial volume averaging. A micro-CT slice is comprised of voxels. Partial volume averaging occurs when materials of different density (i.e. bone and air) occupy the same voxel. The CT (grey) value assigned to each voxel represents an average of the linear attenuation coefficients (i.e. density). This leads to a blurring of the bone non-bone boundary. Hence the actual profile along a row of voxels, solid black line on chart, is represented by a profile more like the dashed line.

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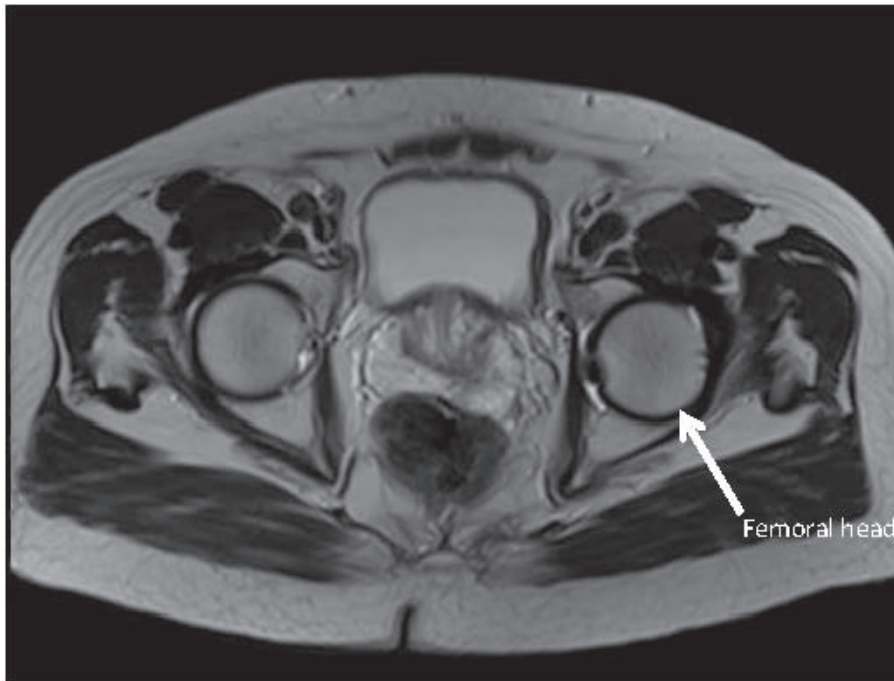
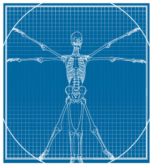


Figure 4: MRI cross section at the level of the femoral head, in which the bone mass and structure is not clearly visible.

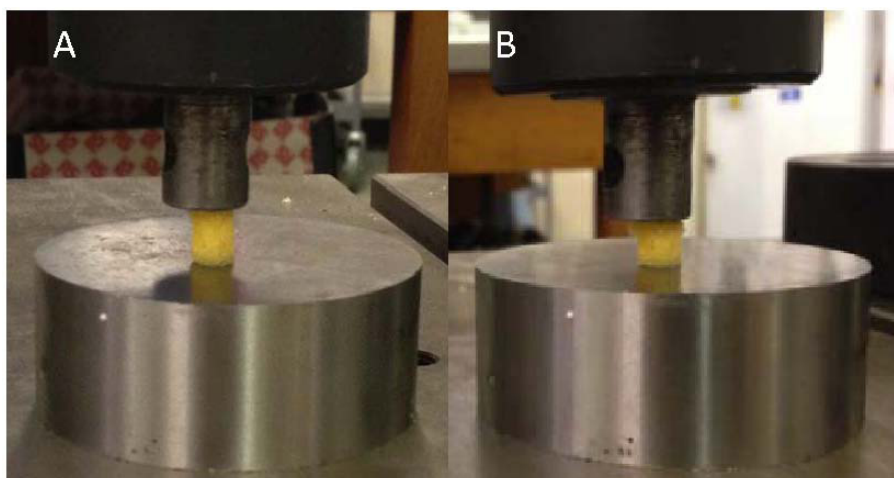


Figure 5: Femoral head trabecular core (A) before and (B) after compression testing. The rig measures mechanical properties such as strength and stiffness which can be used to quantify bone quality and perhaps to calculate whole bone fracture risk.

elements (Figure 1). Femoral strength was experimentally measured using a side impact test to simulate a lateral fall on the greater trochanter. The forearms were biomechanically tested in a fall simulation using a uniaxial testing machine and the maximum failure load (i.e. ultimate strength)

was recorded. Multiple regression models were used to determine which variables best predicted bone strength. Correlation coefficients for trabecular structural measures with femoral and radial bone strength amounted to between $r = 0.428$ and $r = 0.740$. The single best predictors of

strength respectively for CT and MRI based data were apparent trabecular separation ($r^2=0.511$) and bone volume fraction ($r^2=0.548$), which were only moderate correlations. However, by also including measures of bone mineral content collected using DXA scans (e.g. Figure 6) the authors were able to improve $r^2=0.760$ for CT and $r^2=0.7744$ for MRI. Hence apparent trabecular morphology alone was only able to explain 50–55% of the variation in bone strength, but the inclusion of areal bone mineral density increased this to as much as 77%.

These results suggest that low-resolution (i.e. > 0.3 mm voxel size) 3D scanned data were not useful for predicting bone strength. However, this may be due to the particular measurement techniques. The 2D histomorphometric measures that were applied in 2D are known to be inaccurate in comparison to 3D data, even when collected at higher resolution. Micro-CT imaging would have been more useful for imaging trabecular micro-architecture (Figure 7). More importantly the increase in explained variation with the inclusion of mineral content suggests that using the 3D image data it was not possible to tease apart the volume of bone and its mineral content. Due to volume averaging the voxels blurred out the trabeculae, thus it was possible to get the same grey value representing either a large volume of bone with low mineral content or vice versa. Essentially any successful voxel based measure might need to be able to separate the effects of bone volume and mineral density. This may only be achievable at much smaller voxel size e.g. 0.020–0.200 mm. A study that validates low resolution measures of structure and density distribution against high resolution is therefore required.

Given that low-resolution analyses of bone structure alone were not able to strongly predict bone strength, it may be necessary to measure mechanical properties more directly. For example, using micro-CT scans to

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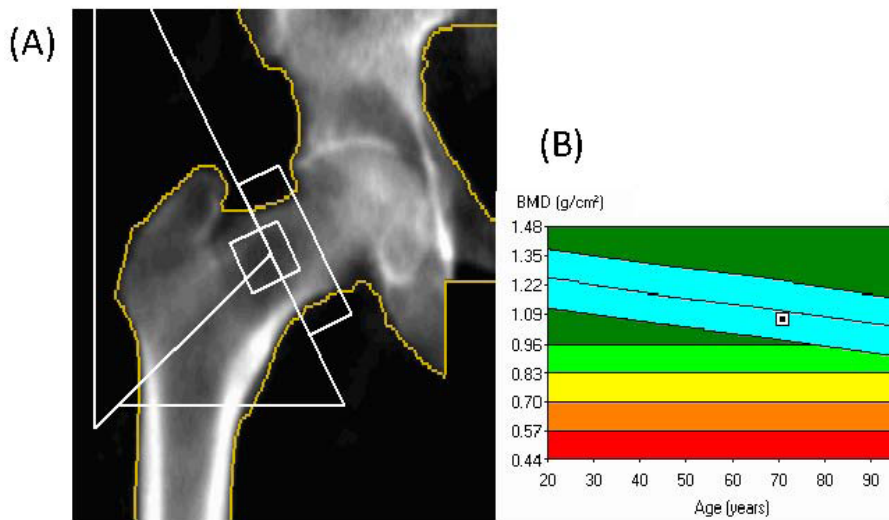
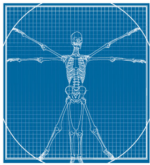


Figure 6: (A) DXA scans measure (B) bone mineral density (BMD) but not structure. Since structure accounts for 40–50% of bone strength the BMD data is not highly correlated with bone mechanical properties or fracture risk.

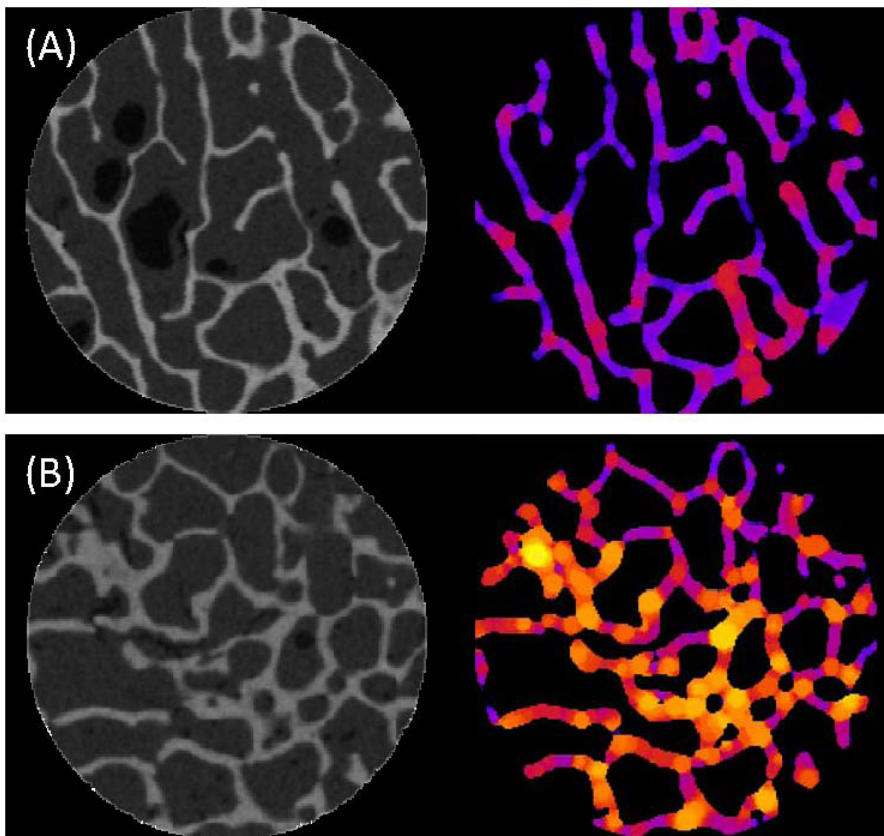


Figure 7: Micro-CT scans are excellent for visualising, measuring and describing trabecular architecture e.g. thickness. Micro-CT scans of (A) osteoporotic and (B) osteoarthritic femoral heads were compared using *BoneJ* which can display thickness as a heat map which is easy to understand. For example, note that the osteoarthritic trabeculae are thicker and better connected than the osteoporotic elements.

create computer models of bones and estimating whole bone strength by simulating loading. Several researchers have used voxel based finite element²⁵ modelling to predict the compressive strength of bone (see Figure 8). Crawford and colleagues²⁶ examined clinically-CT scanned vertebrae with a large voxel size of 0.674³ mm. The scans were used to create 3D models of the bones that could be ‘virtually’ loaded on the computer (using finite element analysis). The (finite element) model was essentially a mesh that described variation in bone volume and mineral density. Importantly the models were constructed from the CT scans using automated algorithms programmed by the authors. After scanning, the ultimate compressive strength of the vertebrae was measured experimentally using a mechanical testing rig. The authors reported that the model predicted 86% of the variation in compressive strength. Thus it appears as though computer modelling could be used to accurately quantify bone strength non-invasively. Fracture loads can be predicted more accurately using 3D computer modelling than DXA data^{27–28}. Furthermore, given that the scans were very low resolution and therefore quick to collect and given that the mechanical modelling was automated it is entirely feasible to use the method in a clinical setting.

Several studies have also used *in vivo* MRI scans to create finite element models for analysing bone mechanical properties^{29–31}. Unlike the CT based studies described above the models were not validated using physical mechanical test data. Since the voxel sizes were large (0.410 to 1.0 mm slice thickness) such a step would be necessary. To date only one *in vivo* MRI based study has attempted to corroborate the computer modelled mechanical properties, comparing values measured using *hrMRI* and micro-CT as the gold standard³². Cadaveric distal tibia were MRI scanned at 0.160³ mm voxel size but the resolution of the

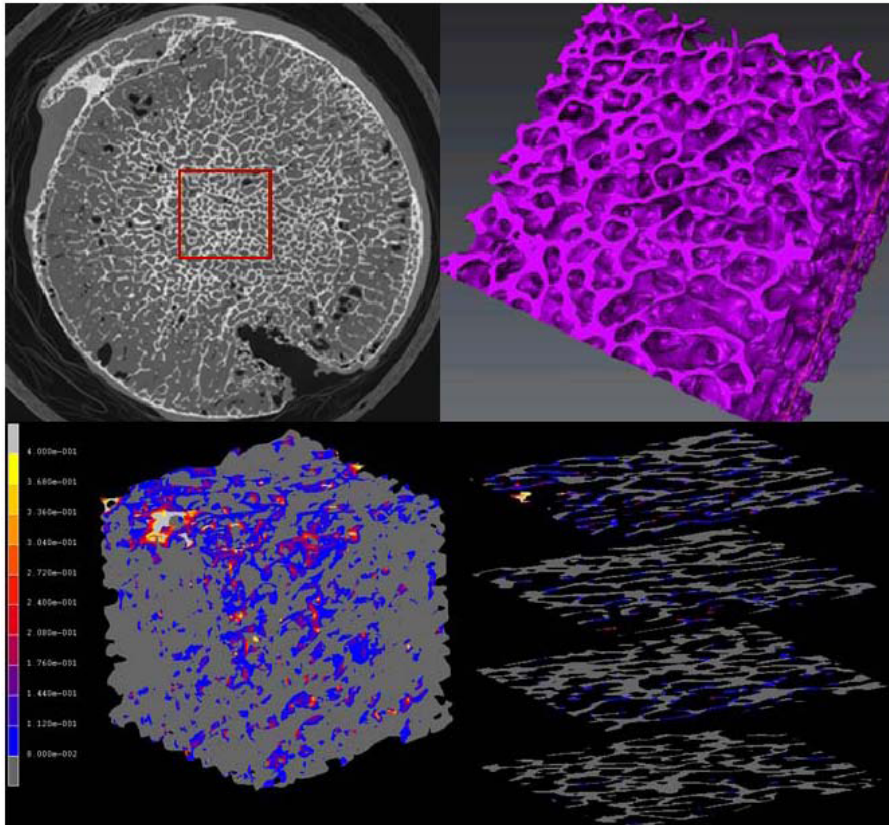
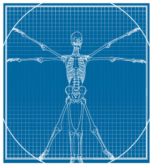


Figure 8: Finite element analysis is a computerised version of mechanical testing. (A) A CT scan is imaged and used to (B) build a 3D computer model of the bone, or a volume of interest within. (C) The model is ‘virtually’ loaded, typically in compression or tension and (D) the stress/strain distribution is quantified.

micro-CT data was higher 0.250³ mm. Trabecular stiffness and elastic moduli (i.e. ability to withstand a load without deforming) were computed. Stiffness measures calculated using the two modalities were highly correlated ($r^2=0.96$) whilst elastic moduli were not ($r^2=0.58$). The authors concluded that *in vivo* MRI scans could probably be used to measure some mechanical properties accurately. Further testing and validation, preferably against experimental data is required to determine what information can be obtained, and which measures would be the most useful.

Applying bone quality in a clinical setting

In order to guide research into metrics for bone quality it is necessary to

consider the end clinical uses. A better understanding of bone quality could improve the identification, diagnosis, monitoring of pharmacological treatments and surgical interventions of patients with fragile bone³³. The holy grail of would be a predictive test for osteoporotic fracture risk. For example, the 10-year probability of fracture is the most desirable measurement to determine intervention thresholds³⁴. As yet though there are no studies demonstrating prospective fracture risk prediction³⁵.

Predicting 10-year fragility fracture risk

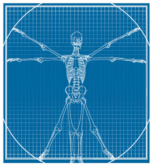
Osteoporotic or fragility fractures due to poor bone density are estimated to affect 200 million people worldwide³⁶ and 300,000 patients in

the UK alone³⁷. Yet the condition is substantially under diagnosed and under treated^{38–41}. Furthermore the situation is getting worse. A study based in Canada revealed that between 1996 and 2002, the number of patients diagnosed with osteoporosis and receiving treatment increased from 6.1% to 12.3%, but then steadily declined to 5.9% by 2008⁴². As UK life expectancy increases and the population ages the number of fractures is expected to rise dramatically⁴³. Recently there has been move by the WHO to set up tools such as FRAX (www.shef.ac.uk/FRAX/). The computer driven system uses algorithms to process patient specific data and calculate the 10-year probability of an osteoporotic fracture. Patients fill a questionnaire on family history and lifestyle as well as bone quality quantified as BMD using a DXA scan (Figure 6). Recent studies have shown that although the system is reasonably accurate the algorithms tend to underestimate the risk of fracture in women, particularly those in the most at risk group over 65 years^{44–45}. Improved metrics for bone quality collected from 3D CT scans could increase the predictive power of FRAX. Specifically measures of mechanical properties based on morphological data or validated finite element models for loading bones virtually.

Monitoring pharmacological treatments

Aftercare in osteoporotic fracture also focuses on improving bone quality to prevent further fractures through various pharmacological means (e.g. calcium, vitamin D and more recently bisphosphonates). After identifying bisphosphonates patients with fragile bones repeat clinical CT scans could be used to monitor disease progression and/or monitor pharmacological treatment outcomes. For example, bisphosphonates are highly effective in the treatment of osteoporosis. Numerous large clinical trials have demonstrated their

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efficacy in reducing bone turnover, increasing bone mass and mineral density and reducing fracture risk. Consequently bisphosphonate therapy, in particular alendronate, has become the mainstay of bone fragility treatment since 1995. However, treatment is associated with insufficiency stress fractures after long-term treatment e.g. 5–10 years⁴⁶. At least in part due to accumulation, propagation and merging of micro-cracks (Figure 9). Many studies have demonstrated that bone mass plateaus after 3–5 years of therapy^{47,48} but, if treatment ceases, there can be a slight loss⁴⁹. Therefore CT based measures of fragility fracture risk could potentially be used to set treat to target criteria for bisphosphonate therapies, monitor progression, identify the time point at which the effect of the drug starts to slow or increase stress fracture risk (Figure 9) and implement treatment holidays. Bisphosphonates are known to stay active in the body for up to 7–10 years after treatment⁵⁰ but holidays will help minimise the risk of fracture complications.

Informing surgical interventions

When osteoporotic fractures do occur patients present with specific technical challenges because of the difficulty in obtaining secure implant fixation. Assessments of bone quality obtained before interventions could be used to inform implant and surgical choices. For example, neck of femur fractures can be fixated but only if the bone is strong enough to hold the screws. Reduced cortical and cancellous bone mass decreases the ability of screw threads to gain purchase, which hugely decreases pullout strength and results in increased implant failure⁵¹. Surgeons could assess a patient's suitability for a screw fixation by using an image-based assessment of bone quality. When screws will not hold, other implant designs such as total hips with acetabular and femoral components are usually more appropriate.

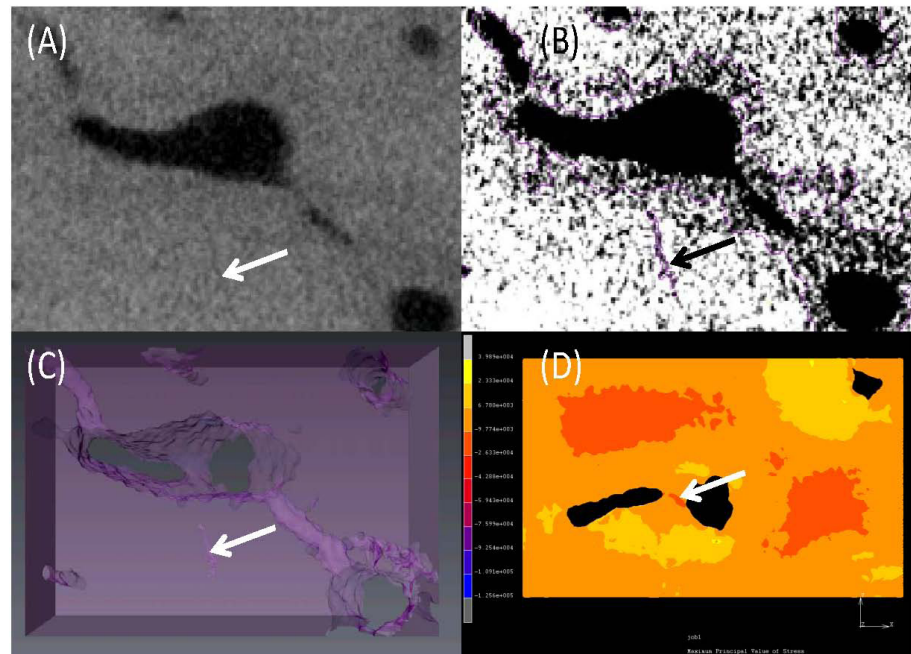


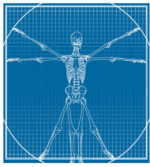
Figure 9: Bone micro-cracks (white arrows) and are repaired by remodelling. Bisphosphonates suppress turnover, particularly bone resorption, leading to increased bone mass. However, over-suppression leads to accumulation of micro-cracks. Micro-cracks can be imaged using (A) nano-CT scans and (B) thresholding the crack void (C) in 3D. (D) An FE analysis of the micro-crack, based on the scan, revealed high stress concentrations at the tip which could cause the crack to propagate.

After fracture fixation or implantation the components need to osseointegrate but osteoporosis alters the biomechanical properties of bone, making tissue stiffer and more brittle. Consequently the load transmitted at the bone-implant interface can often exceed the strain tolerance of osteoporotic bone⁵¹ causing micro-damage that leads to micro-fracture, resorption of bone, implant loosening and subsequent implant failure³⁶ which could happen within months after surgery. In the long term there is potential for disease or patient matched implants to be built that replicate the biomechanical properties of bone that could be quantified using CT based finite element analysis. In the short term there is a need to develop a follow up protocol to identify patients that exhibit resorption before the implants fail, perhaps using 3D imaging data. Those patients exhibiting such failure potential

would need to be restricted in terms of loading the bone-implant construct early and have earlier repeat surgical intervention and augmentation of fixation if required. The main drawback of CT in this respect is that the x-rays cannot penetrate metal, which introduces streak artefacts and noise, blurring the image and making analysis of bone shape and mechanics very difficult. MRI is even less suitable because the use of a magnetic field prevent patients with metallic implants from being scanned.

Clinical-CT scans collected preoperatively that describe 3D variation in bone quality around a fracture site could be used by surgeons to select the most appropriate implant and the locations at which screws or nails should be fitted to achieve the best osseointegration. Patients with enough healthy bone tissue should have standard fixation modes to prevent excessive rigidity that may in

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turn delay bone healing. While regions of poor bone quality will benefit from fixed angle devices like locking plates and screws to improve fixation. Various locking plates have been developed for the common fragility fractures. The key change over conventional devices was the coupling of the screw to the plate, achieved by conically shaped threads in the screw head matching threads in the plate, which allows the screw to effectively bolt into the plate. The singular stable screws prevent load concentration at a single bone-screw interface by distributing load more evenly⁵². Similarly intramedullary nails and other relative stability techniques, such as dynamic hip screws, have been successfully employed to treat complex proximal femoral fractures in the elderly⁵³. Buttressing a fracture by applying force at 90 degrees to the axis of a potential deformity (thereby providing a construct that resists axial load) is an effective method in metaphyseal osteoporotic fractures because it reduces strain at the bone implant interface⁵³.

Conclusion

The understanding of what constitutes bone quality and how it can be measured may lead to better predictions of fracture risk, as well as improved diagnosis, management, treatment, and monitoring of patients with fragile bone. Non-invasive methods are restricted to low-resolution whole body scans or high-resolution peripheral scans as yet. Clearly research needs to be directed to improving imaging technology. High-resolution CT and MRI systems are already becoming available on the market. However, radiation dosage, resolution scan time and cost are always going to be limiting factors no matter how much equipment improves. Accordingly it is essential that researchers find ways of quantifying bone quality at the lowest possible resolution. Even at sub-

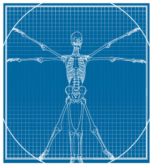
optimal resolution bone quality could be characterised by measuring one or more of the structural and material aspects of bone, or by calculating the mechanical properties more directly using computer models. If the technique is going to translate into a clinical setting it will also be necessary to create an automated computerised system. One that can collect a scan of key fracture sites, automatically generate a 3D finite element model, virtually load the bone and provide relevant mechanical data is an immediate possibility. The data can then be used to inform primary and secondary care of patients. Mechanical properties could be entered into a FRAX (or similar) system, in place of BMD measures. Surgeons could utilise 3D maps of bone quality distribution to plan interventions, select implant type and the optimal location for screws.

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