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Novel Computed Tomography-based Metric Reliably Estimates bone Strength, Offering Potentially Meaningful Enhancement in Clinical Fracture Risk Prediction

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Abstract

Osteoporosis with resultant fractures is a major global health problem with huge socio-economic implications for patients, families and healthcare services. Areal (2D bone mineral density (BMD) assessment is commonly used for predicting such fracture risk, but is unreliable, estimating only about 50% of bone strength. By contrast, computed tomography (CT) based techniques could provide improved metrics for estimating bone strength such as bone volume fraction (BVF; a 3D volumetric measure of mineralised bone), enabling cheap, safe and reliable strategies for clinical application, and to help divert resources to patients identified as most likely to benefit, meeting an unmet need.

Here we describe a novel method for measuring BVF at clinical-CT like low-resolution (550µm voxel size). Femoral heads (n=8) were micro-CT scanned *ex-vivo*. Micro-CT data were downgraded in resolution from 30µm to 550µm voxel size and BVF calculated at high and low resolution. Experimental mechanical testing was applied to measure *ex vivo* bone strength of samples. BVF measures collected at high-resolution showed high correlation (correlation coefficient $r^2=0.95$) with low-resolution data. Low-resolution BVF metrics showed high correlation ($r^2=0.96$) with calculated sample strength. These results demonstrate that measuring BVF at low resolution is feasible, which also predicts bone strength. Measures of BVF should be useful for

clinically estimating bone strength and fracture risk. The method needs to be validated using clinical CT scans.

Keywords: Osteoporosis, Fragility Fractures, Bone Mineral Density, Bone Volume Fraction, Computed Tomography.

Introduction

Osteoporosis is a systemic condition characterised by compromised bone strength due to abnormality in the amount and/or architecture of bone. The consequence of osteoporosis is a heightened risk of fragility (low trauma) fractures, the outcomes of which are serious morbidity and death (1). The disease is a grave public health concern and estimates suggest that ~200 million people are affected worldwide (2, 3). At present, osteoporosis and associated fracture risk are assessed clinically in terms of bone mineral density (BMD) assessment performed by dual energy x-ray absorptiometry (DEXA). BMD refers to the bone mass per unit area and is employed as an indirect indicator of fracture risk (1). Importantly, BMD does not reflect bone quality, which is an integration of several features influencing skeletal resistance to fractures.

Bone quality depends upon material and structural factors including but not limited to mineralisation, quality of collagen, rate of bone turnover, cortical geometry and trabecular micro-architecture (including trabecular number, thickness, orientation and connectivity) (4, 5). The ability of bone to resist fracture depends not only on the amount of bone but also the spatial distribution of bone mass and the intrinsic properties of the materials that constitute bone which come under the wide ranging concept of bone quality. Bone strength reflects the combination of bone mass and bone structure (6). BMD testing only measures the areal bone mass and does not capture any structural information because images are 2D. Thus BMD is not an adequate surrogate marker of bone strength; it only explains about 50 % of *ex vivo* strength (7).

Given the high socio-economic relevance of fragility fractures, there is a need for a clinical method that can detect specific traits of bone fragility more efficiently than the conventional DEXA-measured BMD. Development of such improved measures of bone strength can allow for identification and assessment of rapidly occurring skeletal changes seen with pathological or age-related deterioration in bone health. 3D imaging techniques including micro-computed tomography (micro-CT), are employed for assessing bone strength *ex-vivo* but are of limited clinical use at present owing to radiation hazards as well as technical issues, high costs and accessibility (8-10). Micro-CT enables *ex vivo* evaluation of various parameters such as volumetric bone mass (expressed as bone volume fraction 'BVF'), which has been identified as a strong determinant of bone strength ($r^2 > 0.8$) (11, 12).

Low-resolution clinical-CT is a non-invasive and accessible imaging technique available to most hospitals. 3D measures such as BVF derived from clinical-CT scans are potentially a useful option for estimating bone strength. Clinical-CT derived measures of skeletal morphology may be especially useful in cancer patients because these patients undergo CT scans for staging the disease and planning treatment, potentially offering low cost, easily accessible and safe technology for predicting bone strength (13).

Aims

To devise a method for measuring BVF of the femoral head trabecular bone at a low resolution (550 μ m voxel size; i.e. comparable to clinical-CT resolution), validate the method against high-resolution (30 μ m voxel size) micro-CT data and determine whether the BVF metrics calculated at low resolution relate to bone strength.

Materials and Methods

Femoral head samples (n=8) were collected post-operatively from patients giving informed consent undergoing hip arthroplasty for osteoarthritis at the Department of Orthopaedic Surgery, Imperial College Healthcare NHS Trust, UK and were obtained from the Imperial College Healthcare Tissue Bank (ICHTB; ref:13004 issued from sub-collection ref:MEDA). ICHTB is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London and approved by the National Research Ethics Service (NRES) to release human material for research (12/WA/0196).

Femoral heads were micro-CT scanned at the Natural History Museum, London, UK using a Nikon (Metris X-Tek) HMX-ST 225 CT system (Nikon Metrology, UK) (14). Specimens were fixed on a styrofoam base and placed onto a turntable inside the scanner for scanning at set parameters of 180kV and 165 μ A with a 0.1mm copper filter. A total of 6315 projections were collected at an angular interval of 0.057°. The resulting scan for each femoral head had 2000 serial cross-sectional views with a cubic voxel size of 30 μ m. Scans were reconstructed using CT Pro 2.2 (Metris X-Tek, UK) and converted to the DICOM (Digital Imaging and Communications in Medicine) file format using VG Studio Max 2.0 (Volume Graphics, Heidelberg, Germany). Data were collected on external hard drives (NTFS format) and analyses were performed on a high power workstation (HP Z800) at the Musculoskeletal Lab, Imperial College London, UK using the BoneJ plugin for bone image analysis in ImageJ software (Java image processing program) (15).

The micro-CT DICOM data files were imported into ImageJ and downgraded in resolution from 30 μ m to 550 μ m voxel size (Figure 1a, 1b). Spheres of trabecular bone were virtually sectioned from all the high and low-resolution 3D scans of the femoral heads using the sphere fitting algorithm in BoneJ. The largest sphere possible was collected about the centre of the femoral head. Frequency distribution plots of the voxel grey values were plotted using the 'histogram' function in ImageJ. Threshold grey values were calculated by finding the trough that separates bone and non-bone peaks (16, 17). Based on this value, a black and white binary image was generated using the 'threshold' function in ImageJ. Trabecular BVF was measured by counting voxels representing bone. The accuracy of lower-resolution metrics was validated against the high-resolution data by plotting scatter graph and calculating correlation coefficient (r^2).

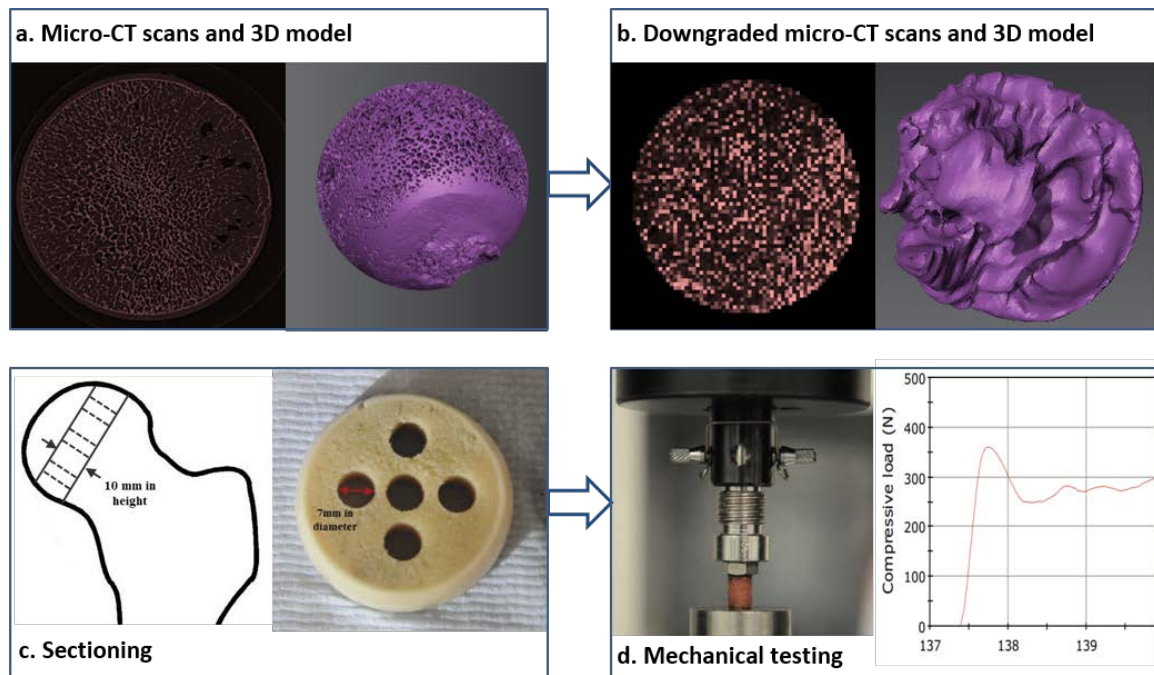


Figure 1 a. A slice of high resolution micro-CT scan and 3D model of femoral head built from it, BVF was measured from these high resolution scans; b. High resolution micro-CT scans were downgraded in resolution from 32 μ m to 550 μ m; 3D model of femoral head built from the low resolution scans, BVF was measured again at low resolution; c. Five cylindrical sub-samples (7mm in diameter, 10mm in height) were sectioned from the locations shown above; d. Two sub-samples were chosen randomly and compressively tested to failure for calculating mechanical strength, mechanical behaviour can be seen from load-displacement graph.

Five cylindrical sub-samples (10mm in height and 7mm in diameter) were drilled from each femoral head (Figure 1c). Two sub-samples from the five were selected randomly and mechanically tested until fracture under uniaxial compressive loading (Figure 1d) using an Instron 5565 mechanical test machine (Instron Engineering Corporation, USA) at the Department of Mechanical Engineering, Imperial College London, UK. The maximum load (the peak at mechanical behaviour

graph shown in Figure 1d, which corresponded with fracture) divided by specimen cross-section, was used to calculate the bone strength of each cylindrical specimen (18).

Results

BVF data collected at high resolution (30 μ m voxel size) were correlated with BVF data at low resolution (550 μ m voxel size). A high positive correlation ($r^2=0.95$) was seen between BVF measures at high and low resolutions (Figure 2).

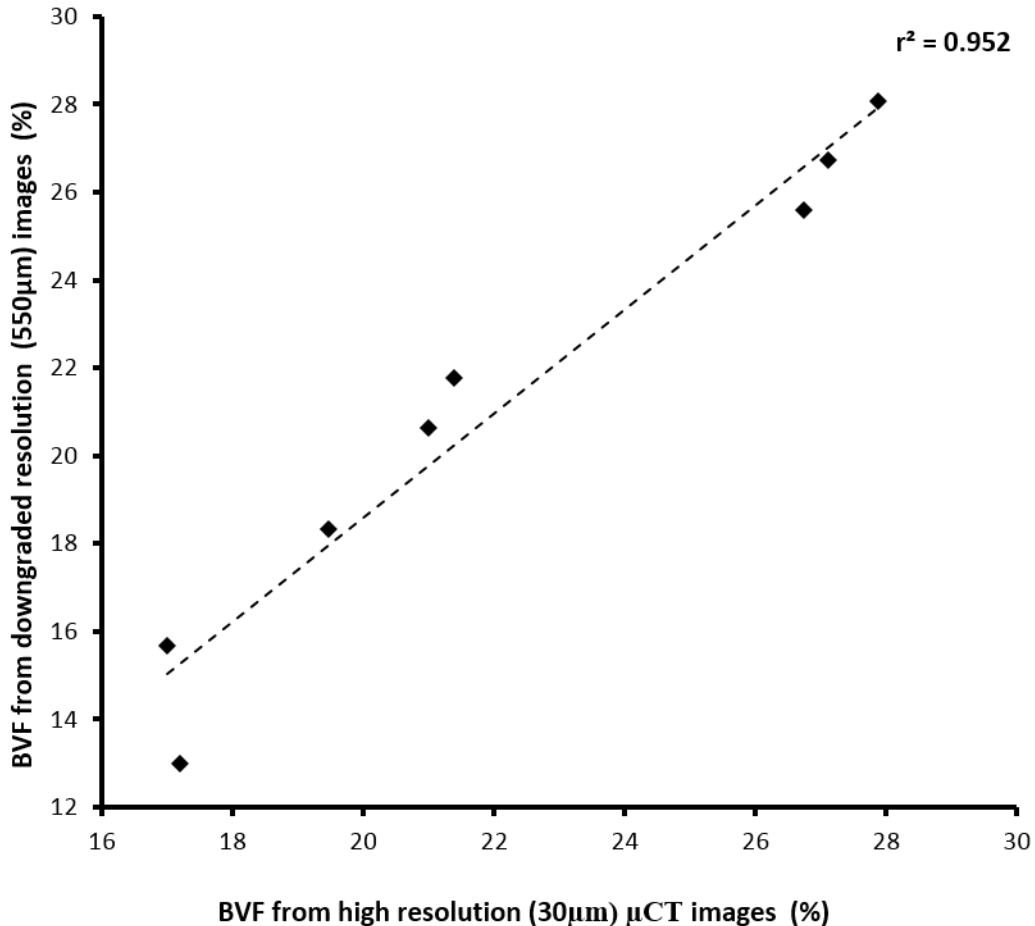


Figure 2. Bone volume fraction (BVF) measured from downgraded resolution images correlated with BVF measured from high-resolution μ CT images

The low-resolution BVF metrics were correlated with the means of the compressive bone strengths calculated *ex vivo* for the two cylindrical specimens from each femoral head. A high positive correlation ($r^2=0.96$) was observed between low-resolution BVF measures and *ex-vivo* bone strength (Figure 3).

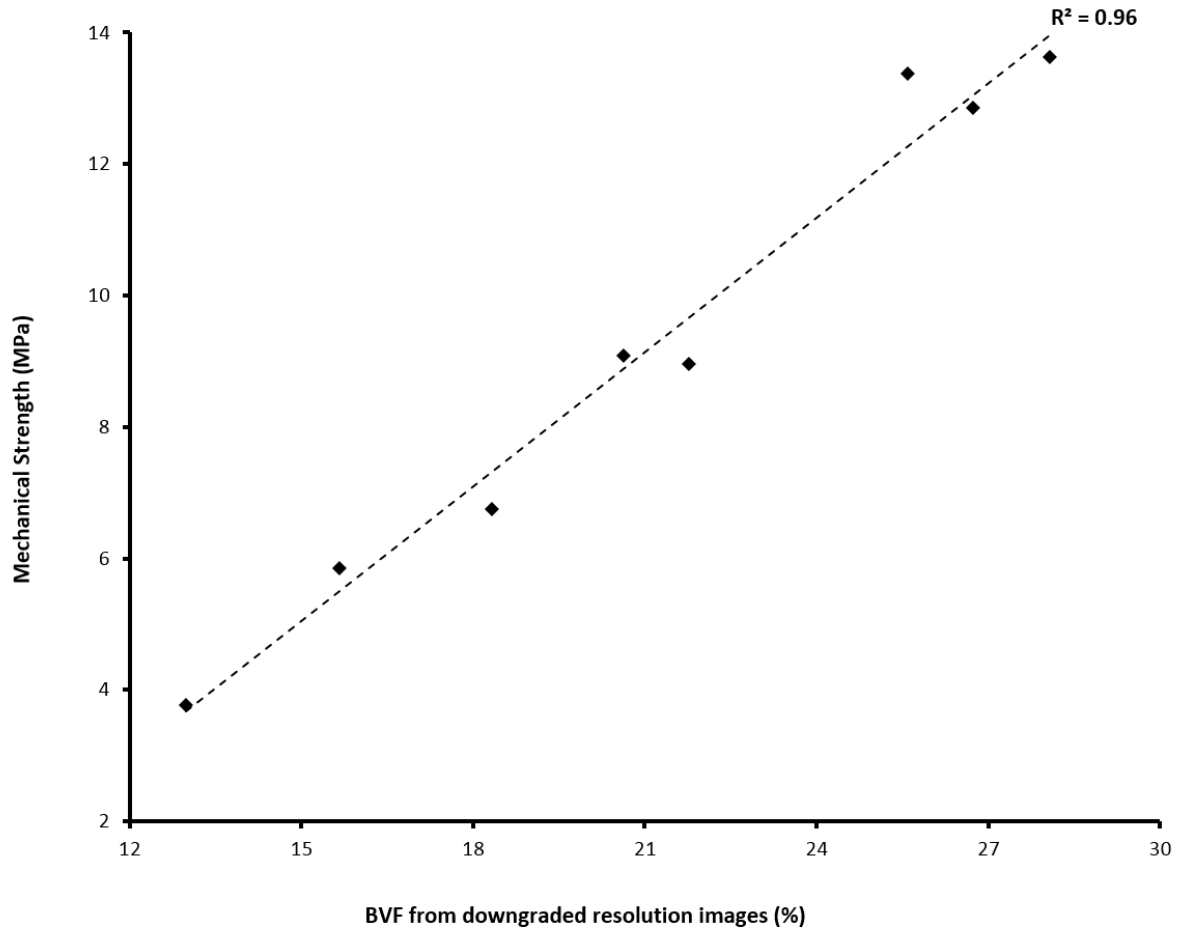


Figure 3. Mechanical strength correlated with bone volume fraction (BVF) measured from downgraded resolution (550 μ m) images

Discussion

BMD measurement using DEXA is the current mainstay for assessing osteoporosis and associated fragility fracture risk (1). However, the 2D DEXA technique only allows for areal measurement of bone mass and does not take into account the contribution of other characteristics such as volumetric bone mass and micro-architecture to bone strength (6). 3D techniques such as high-resolution micro-CT have been used to calculate BVF *ex vivo* but are clinically inapplicable currently due to high radiation exposure (9). Therefore this study explored the potential of using low-resolution clinical-CT for estimating bone strength as most oncological patients receive CT scans clinically for staging tumours and planning interventions.

The study has demonstrated that femoral head trabecular BVF can be calculated (> 95% correlation with BVF measured from high-resolution micro-CT images) from CT images downgraded in resolution comparable to clinical-CT scans of the pelvic region. BVF metrics from these low-resolution scans were also shown to have a 96% correlation with bone strength assessed *ex vivo*. These findings are concordant with results reported by Nazarian et al. who studied biopsy specimens of trabecular bone from spine and/or femur of patients with metastatic prostate, breast, lung, ovarian, or colon cancer (n=41) and non-cancer cadaveric samples (n=96). Specimens were imaged using micro-CT and mechanically tested by uniaxial compression. Measured BVF was shown to account for 84% of bone strength variations in all trabecular bone specimens irrespective of the skeletal site or pathology (12).

The results of the present study show that it is feasible to measure BVF at large voxel size (550 μ m), which is the resolution offered by modern clinical CT scanners. The calculated low resolution measures of BVF are also highly predictive of bone strength assessed *ex vivo* (96%

correlation) whereas BMD has previously been shown to have only a 50% correlation to bone strength (19).

A limitation of the study is the use of low-resolution data downgraded from high-resolution micro-CT data as a simulation of low resolution clinical-CT data. The micro-CT data do not contain the same noise and artefacts that are present in clinical-CT data. Further work using actual clinical CT data for determining BVF and its comparisons with BMD values from DEXA and 'Finite Element Analysis' measures of mechanical behaviour of bone is required to provide more conclusive results (20). Future investigations showing that such clinical CT-based measurements predict fractures better than the current methods may help establish the potential future use of BVF as an easy access, non-invasive and cost-effective method for clinical bone health assessment.

Conclusion

BVF may readily serve as an effective metric for predicting bone strength in cancer patients who routinely undergo CT scans of the pelvis as part of their cancer management regime and changes in bone strength over time can be tracked using BVF measures derived from those CT scans. Timely and accurate identification of high risk patients such as those with diminishing BVF can allow clinicians to modify treatment and/or prescribe bone sparing agents (21). Clinical trials of diet and/or exercise intervention for improving bone health can potentially utilise BVF instead of BMD (22, 23). With advancements in CT technology leading to fall in radiation dosage, this novel metric of bone strength could find widespread clinical use in the future for diagnosing osteoporosis in the general population, predicting fracture risk and monitoring treatment outcomes.

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