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EDITORIAL

Osteoporosis: current screening methods, novel techniques, and preoperative assessment of bone mineral density

K. Al-Hourani,
S-T. J. Tsang,
A. H. R. W. Simpson

From University of Edinburgh, Edinburgh, UK

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Osteoporosis is "a disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk".[1] While it is known to be a multifactorial metabolic disease of the bone,[1] the exact pathoaetiology remains unclear.[2] One recent development is the 'gut-bone axis' theory which proposes a critical role of the gut microbiome and its metabolites in the development of osteoporosis.[2,3] It is defined radiologically as a dual energy X-ray absorptiometry (DXA) score > 2.5 standard deviations below the young adult mean.[1] It is estimated that there are 2.7 million fragility fracture presentations annually within the European Union, culminating in €37.5 billion in healthcare costs.[4]

The clinical significance of osteoporosis is the resulting risk of fracture. Osteoporotic fractures requiring hospital admission have been shown to have an increased length of stay, increased risk of nosocomial infection, and psychosocial ramifications.[5] This is in addition to an increased risk of mortality, particularly for vertebral and hip fractures.[5] More recently pre-clinical studies have demonstrated impaired fracture healing secondary to inflammatory dysregulation.[6] One proposed mechanism is a failure of fibrinolysis of the fracture haematoma preventing angiogenesis and progression to fracture union.[7]

Current screening methods

The National Institute of Clinical Excellence in the UK recommends fracture risk stratification as part of falls assessment for anyone over the age of 65 years in women, or 75 years in men, or anyone under these ages who displays risk factors (e.g. alcohol use, smoking, and previous fragility fracture).[8] However, there remains debate as to how fracture risk should be measured, as some osteoporotic fractures (e.g. vertebral fractures) are not closely correlated to reduced bone mineral density (BMD) in isolation.[9] At present, DXA is the current consensus gold standard.[10,11] By emitting two low-energy x-ray radiation beams, it can estimate BMD by subtracting the attenuation effect from the surrounding soft-tissues.[12,13] DXA scanning has proved to be cost-effective and is a standardized method of assessment.[14] There is also evidence to suggest that DXA scanning is an effective predictor of major fragility fractures (e.g. hip fractures).[15]

While BMD is an essential component of screening, DXA scanning does not take into account other significant material properties, such as the increase in cross-sectional area and changes in organic composition. Organic component evaluation, which DXA does not account for, is therefore vital in measuring 'bone quality'. Hence, measurement of bone quality has been proposed as this encompasses parameters such as BMD, microarchitecture of trabecular bone, microcrack prevalence, bone geometry, and bone matrix material properties.[16] This has led to the development of 3D imaging techniques. One such method is quantitative peripheral CT (qpCT), which is calibrated using solid phantoms (representing various BMDs) and is a measure of true volumetric bone density without the superimposition of cortical bone or an enlarged soft-tissue envelope. Quantitative peripheral CT has been shown to be more sensitive than DXA in the detection of osteoporosis.[17] There are, however, significant limitations to qpCT,

Correspondence should be sent to Khalid Al-Hourani; email: kalhourani@doctors.org.uk

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including lack of standardization, increased radiation exposure, and increased cost.[18]

As a result of the limitations of qpCT, a further method of peripheral assessment of bone quality, which encompasses bone density and microarchitectural morphology (both cortical and cancellous) and its effect on the mechanical integrity of bone, was designed; high-resolution quantitative peripheral CT (HR-qpCT). The radiation dose is significantly reduced, maintaining a reduced scanning time and high precision of BMD assessment.[19] More recently, this has been combined with finite element analysis testing, whereby the HR-qpCT images are converted into finite element blocks within a cubic structure, which models the material properties of bone, followed by simulation of load in order to predict mechanical behaviour. Both of these techniques have been validated.[20] However, qpCT and HR-qpCT remain in their early development stage and are currently used only for research purposes. Additionally, their ability to monitor longitudinal changes has been questioned as changes in quantitative CT have yet to be correlated with clinical outcomes.[21]

The role of MRI in the evaluation of osteoporosis has also evolved, largely due to the assumption that there is progressive adipose involution of bone marrow with osteoporosis. Varying methods have been proposed to evaluate the subsequent fat fraction, such as T1-weighted imaging, diffusion weighted imaging, and proton magnetic resonance spectroscopy.[22] These methods are still under evaluation and not yet available for universal screening.

As a result of concerns regarding radiation exposure and the problem of lack of portability, quantitative ultrasound scanning of the calcaneus has been studied.[23] While this is non-ionizing and portable, it has not yet been validated and its accuracy is reduced in patients with inflammatory disease.[24] Currently there is no agreed diagnostic criteria for this technique and it is not yet recommended for screening of osteoporosis.

Novel techniques

Bone is a composite material, however DXA only quantifies the mineral content, neglecting the organic component. Impairment of the organic component of bone decreases its toughness, resulting in brittleness. Early work has been undertaken to evaluate the ability of spectroscopy to detect osteoporosis. One such method is Fourier Transform Infrared Spectroscopy, whereby the metabolic changes associated with osteoporosis can be detected, namely by estimating the relative abundance of trace metabolites of both the organic and inorganic constituents of bone using infrared radiation.[25] More recently, X-ray dark-field vector radiography (XVR) has emerged as a new alternative approach in the assessment of bone strength. An XVR image is formed through the mechanism of small angle scattering and is compatible with conventional X-ray tube sources, efficiently yielding high-quality dark-field scatter images. Not only is this able to provide imaging of bone microstructure, but it is also able to yield information on associated bone strength by estimating the anisotropic properties of bone.[26]

At present, none of the above techniques are routinely available in the acute trauma setting. As a consequence, measurements of bone material properties are not available pre-fracture fixation and cannot be used to guide surgical management. One technique that is readily available is estimation of cortical bone thickness. Cortical bone carries a considerable part of the physiological load, and previous studies have shown that structural behaviour of whole bones is determined by the contribution of cortical bone.[27] Therefore, correlation of cortical bone with bone properties could provide an accurate, rapid, and inexpensive method for predicting those at risk of osteoporotic fracture. It would also have the advantage of being available preoperatively and therefore could help guide choice of surgical fixation.

In this month's edition of *Bone & Joint Research,* two studies have evaluated the accuracy of cortical bone thickness for the estimation of BMD. Firstly, Schmidutz et al[28] estimated the correlation between cortical bone thickness of the distal radius on plain radiographs and predicted BMD from DXA and HR-qpCT. Using measurements from cadavers of human forearms, Schmidutz et al[28] found that cortical bone thickness of the distal radius had a good correlation with local DXA ($r = 0.78$, $p < 0.001$) and moderate correlation with local HR-qpCT ($r = 0.63$, $p < 0.001$). Estimation of cortical bone thickness of the distal radius was modified from the techniques previously described by Tingart et al[29] and Mather et al.[30] Intraobserver (0.83 to 0.92, $p < 0.001$) and interobserver (0.79 to 0.86, $p < 0.001$) variation for this modified technique was found to be excellent. In the second study, 54 consecutive patients with distal radius fractures underwent standard posteroanterior and lateral plain radiographs with an aluminium step wedge and DXA. Cortical bone thickness of the distal radius had a low correlation coefficient ($r = 0.34$ to 0.52) with DXA.[31] Inclusion of an aluminium step wedge alongside the wrist for calibration allowed an estimate of density to be obtained, which was found to have a better correlation ($r = 0.65$) with forearm DXA values. However, it should be noted that only 27/54 underwent DXA of the hip and lumbar spine, of which only 13 underwent DXA of the contralateral forearm. Once again, interobserver reliability for estimation of cortical bone thickness was found to be excellent (0.82 to 0.96).

Future research

While these novel and simple techniques provide clear advantages, they are yet to be validated and translated into clinical practice. This primarily relates to the inability to predict fracture risk. It is unclear if cortical

bone thickness alone can provide early detection of a reduction in BMD, as bone loss in early osteoporosis is mainly trabecular in nature, with later cortical porosity and increase in endocortical surface.[32] This would need to be correlated with an accurate form of in vivo cross-sectional imaging, due to microstructural and biomechanical differences between live and cadaveric bone.[33] Additionally, the ability to predict fracture risk using simple measures requires an international consensus definition on standardized clinic measurement and reproducible cut-off values. A promising area of research, which may have widespread effects on mass screening, is the application of artificial intelligence through machine-learning or artificial neural networks. The advantage of artificial intelligence is that mass screening through big data becomes feasible. This uses the concept of radiomics, whereby pixel classifier algorithms are used to perform quantitative analysis of plain radiographs to create prediction models of fracture risk. This has recently been shown to have high correlation with BMD estimation from DXA scanning.[34]

Nevertheless, preoperative assessment of bone quality could have wide-ranging benefits for patients and healthcare providers. Additionally, in low- and medium-income countries where DXA scanning is not routinely available, the ability to predict fracture risk from a plain radiograph would have great utility. The potential in measuring cortical bone thickness to fulfil these needs has been highlighted in this month's issue of *Bone & Joint Research*.

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Author information:
- K. Al-Hourani, MD FRCSEd (Tr&Orth), Orthopaedic Registrar, Department of Trauma and Orthopaedics, Royal Infirmary of Edinburgh, Edinburgh, UK.
- S-T. J. Tsang, PhD FRCS (Tr&Orth), Orthopaedic Registrar
- A. H. R. W. Simpson, MA (Cantab), DM (Oxon), FRCS (England & Edinburgh), George Harrison Law Professor of Orthopaedic Surgery

Department of Trauma and Orthopaedics, Royal Infirmary of Edinburgh, Edinburgh, UK; Department of Orthopaedic Surgery, University of Edinburgh, Edinburgh, UK.

Author contributions:
- K. Al-Hourani: Conceptualization, Writing - original draft, Writing - review & editing.
- S-T. J. Tsang: Conceptualization, Writing - original draft, Writing - review & editing.
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