Clinical application to bone health assessment of a new MR-based technique enabling quantitative measurement of trabecular bone structure

Juliet Compston[1], Amanda Cox[2], Michael Stone[3], Jane Turton[3], Irene Debiram[1], and Kristin James[2]
[1]*School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom,* [2]*Acuitas Medical, Swansea, United Kingdom,* [3]*Llandough Hospital, Cardiff, United Kingdom*

Introduction: Osteoporosis is becoming more prevalent—the number of hip fractures is expected to double in the next 50 years due to the aging population [1], and currently costs the NHS around £2 billion a year, a figure which is expected to triple by 2036 [2]. There is high morbidity associated with hip fracture—20% of those individuals sustaining hip fracture will die within 6 months and, of those that survive, only 1 in 3 will ever regain their previous level of mobility and independence [3]. Trabecular bone structure is known to change during osteoporosis, leading to increased risk of fragility fracture [1], but these structural changes are not currently used in diagnosis. DXA, the current gold standard of osteoporosis diagnosis, is not capable of evaluating changes in trabecular architecture [4] though it is thought that trabecular measurement would allow better assessment of fracture risk [5]. A new magnetic resonance-based technique, designed to measure biologic texture too fine to be resolved by conventional MR imaging, was evaluated for its ability to assess bone health through quantification of trabecular bone structure. The technique provides a measure of the characteristic distance between trabecular elements by signal analysis of a finely sampled one-dimensional, spatially encoded echo from a selectively excited internal volume. This analysis yields a spectrum of structural wavelengths present within the selected volume of bone or tissue. A clinical study applying the technique in the L1 vertebrae of 20 postmenopausal women was undertaken, testing its ability to distinguish patients with normal bone structure from those with abnormal. The vertebral body exhibits a larger percentage change in trabecular web structure with onset of osteoporosis, compared to other skeletal sites[6].

Methods: Twenty female postmenopausal women, mean age 64.4 years, who had not been treated with oral bisphosphonates for any longer than 6 months, were recruited for this study. Due to the difficulty in recruiting women with fracture who had not exceeded the time limit on bisphosphonates, the cohort comprised three groups, normal patients (n=6), osteopenic or osteoporotic patients with no fragility fracture (n=6), and osteopenic or osteoporotic patients with fragility fracture (n=8), These were assigned to groups by bone mineral density (BMD) T-score obtained at the lumbar spine and hip, and by fracture history. MR intensity data were acquired along the long axis of a prismatic volume 10mm x 10mm by 70mm, aligned in the LR direction across the L1 vertebral body, via the application of an in-house-developed pulse sequence. The resultant signal intensity profile was then analysed to yield a spectrum of structural wavelengths present along the sampled volume.

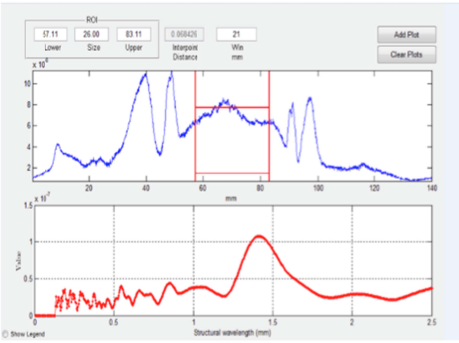

Figure 1. The region along the MR signal intensity profile used for analysis is indicated by the red goal posts overlaid on the MR signal intensity profile (top); bottom is the spectrum of textural wavelengths in mm obtained by fine structure analysis of the selected region.

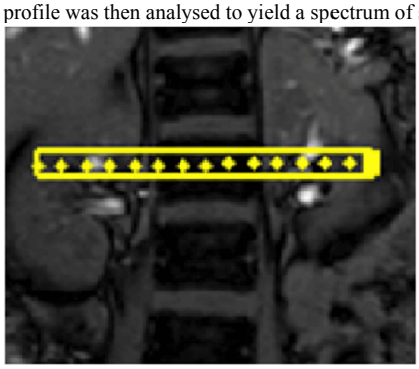

Figure 2. Overlay of prismatic volume along which complex MR echo intensity is measured on reference image of the L1 vertebra.

Data analysis: The prismatic volume selected for excitation was positioned across the vertebral body through use of low-resolution MR reference images. Post scan, analysis was done on a 26mm long region of the acquired profile centred around the midpoint of the vertebral body in the LR direction, to limit the structural analysis to regions of trabecular bone only (see figures 1 & 2). The data were processed using Welch's method [7] with a window size of 21mm to yield wavelength spectra for each patient. The resulting structural wavelength spectra were visually examined to identify differences between the groups in the cohort and a number of biomarkers were devised to separate normal from abnormal bone structure. Statistical analysis, one-way analysis of variance (ANOVA) and correlation of biomarker values with T score, patient age, and BMD, was carried out using the statistics toolbox in MATLAB®.

Results: Clear differences were observed between spectra from osteoporotic or osteopenic patients and women with normal BMD (see figure 3). Biomarkers were developed to draw on these visual differences to provide a quantitative measure of bone health. Four of the developed biomarkers could significantly ($p<0.03$) separate women with normal BMD from those who were osteopenic or osteoporotic. These biomarkers were: 1) position of the highest intensity peak when the spectrum was truncated at 1mm, 2) position of the highest intensity peak when the spectrum was truncated at 2.5mm, 3) difference in intensity of the two highest intensity peaks in the wavelength spectrum, and 4) the average difference in intensity of the two dominant peaks in a set of spectra. All of these showed significant ($p<0.02$) correlation to both T-score and BMD in g/cm^2 but no significant correlation was found with patient age ($p>0.1$) for any biomarker. The biomarkers, when applied to wavelength spectra generated using our fine structure analysis technique, could classify patients with normal or osteopenic/osteoporotic BMD with success rates between 75% and 85%.

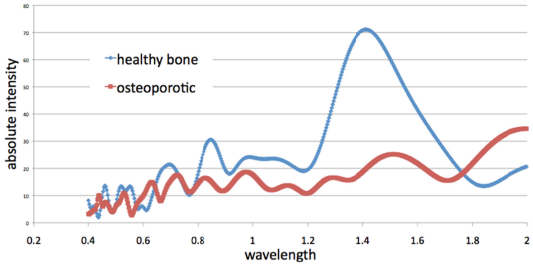

Figure 3. Spectra of fine structural textures generated for healthy (blue) and for osteoporotic bone (red).

Discussion: This clinical study has shown that, using the biomarkers we have identified to date, the new technique of fine structure analysis applied in this study can distinguish between patients with normal and and with osteopenic/osteoporotic BMD, with success rates varying between 75% and 85% depending on the biomarker applied. Advantages of the new technique over DXA are that 1) it does not require ionising radiation and 2) it targets trabecular bone structure rather than just density. This study reports the first steps towards validating this technique as a credible partner to DXA for the assessment of bone health. Future work will focus on refinement of the biomarkers in order to provide increased sensitivity to variations in bone structure indicative of disease progression.

References: 1. WHO study group, Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Report of WHO study group. 1994, Geneva: World Health Organisation.
2. Kirby, J., NHS fracture costs could treble to £6bn, argues charity, in Guardian professional. 2011.
3. Compston, J. and C.J. Rosen, Fast Facts: Osteoporosis. 2006, Abingdon: Health Press.
4. Sornay-Rendu, E., et al., Alterations of cortical and trabecular architecture are associated with fractures in postmenopausal women, partially independent of decreased BMD measured by DXA: The OFELY study. Journal of bone and mineral research, 2007. 22(3): p. 425-433.
5. Keaveny, T. and O. Yeh, Architecture and trabecular bone - Toward an improved understanding of the biomechanical effects of age, sex and osteoporosis. Journal of musculoskeletal neuron interaction, 2002. 2(3): p. 205-208.
6. Merck & Co., Inc. Pathophysiology of bone. 2004; Available from: http://www.merckmedicus.com/pp/us/hcp/diseasemodules/osteoporosis/pathophysiology.jsp
7. Welch, PD, The Use of Fast Fourier Transform for the Estimation of Power Spectra: A Method Based on Time Averaging Over Short, Modified Periodograms. IEEE Transactions on Audio Electroacoustics, 1967, AU-15: p. 70–73.