

Pharmacokinetic Modeling Study on Bone Perfusion of Osteoporosis

H. T. Ma^{1,2}, J. F. Griffith¹, D. K. Yeung¹, and P-C. Leung³

¹Department of Diagnostic Radiology and Organ Imaging, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong, ²Electronic and Information Engineering Department, Harbin Institute of Technology Shenzhen Graduate School, Shenzhen, Guang Dong, China, People's Republic of, ³Jockey Club Centre for Osteoporosis Care and Control, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong

Introduction: Clinical, epidemiological and histological studies have indicated a link between vascular disease and osteoporosis (1). Dynamic contrast-enhanced MRI (DCE-MRI) provides a more direct measure of bone perfusion. DCE-MRI studies have consistently shown how semi-quantitative perfusion parameters are consistently reduced in osteopenic and osteoporotic bone compared to normal bone mineral density (BMD) subjects (2). However, semi-quantitative parameters provide limited information on the physiological processes affected. The purpose of this study, was to apply a modified Brix pharmacokinetic model to the investigation of bone perfusion in subjects of varying BMD with a view to increasing our knowledge of the bone perfusion anomalies occurring in osteoporosis.

Methods: The cohort comprised 165 subjects (65 males, 100 females, age>65 yrs). Both DCE-MRI and ¹H MR spectroscopy was performed on each subject. ¹H MR spectroscopy yielded the percentage marrow fat content of bone. DCE-MRI data were acquired in the mid-lumbar sagittal plane for male subjects and in the transverse plane through the mid-L3 vertebral body region for female subjects (Fig.1). A bolus of gadoteric acid at a concentration of 0.15 mmol per kilogram body weight was injected, followed by a dynamic scanning with a short T1-weighted gradient-echo sequence (2.7/0/95; prepulse inversion time, 400 ms; flip angle, 15°). A region of interest (ROI) was drawn manually encompassing the trabecular bone (Fig. 1), from which a time-signal intensity curve was generated. A pharmacokinetic model (3,4) (Eq.1) was employed to analyze DCE-MRI data.

$$\frac{S(t)}{S_0} = 1 + A \frac{k_{ep} (e^{-k_{el}t} - e^{-k_{ep}t})}{k_{el} - k_{ep}} \quad (\text{Eq.1}),$$
 where S_0 is the baseline signal intensity, $S(t)$ is the

signal intensity change with time, A is the amplitude of contrast uptake into the tissues under investigation; k_{ep} is the rate constant for contrast extraction from interstitial space into the plasma, and k_{el} is the elimination rate constant of contrast from the body. Representative perfusion signal intensity curves were simulated for the three different BMD groups (normal, osteopenia and osteoporosis) and for male and female respectively (Fig.2). Simulation was based on the pharmacokinetic model (Eq.1) and the mean of the quantitative measures, A , k_{ep} , and k_{el} , for each subgroup.

Results: Significant differences were found in pharmacokinetic parameter across different bone density groups with slight gender differences. In male subjects, osteoporotic subjects had lower mean A and k_{el} compared to osteopenic and normal BMD subjects ($p < 0.01$). Product Ak_{ep} , indicating the vessel permeability, was significantly decreased in osteoporotic and osteopenic male subjects. In female subjects, osteoporotic and osteopenic subjects had lower mean A compared with normal BMD subjects ($p < 0.01$), while product Ak_{ep} was largest in osteopenic subjects and smallest in normal BMD subjects.

According to the model algorithm (Eq.1), the relative signal intensity for different BMD groups in Fig.2, with osteoporotic subjects having a flatter curve than normal BMD subjects, especially during the wash-out phase.

Discussion: The first main finding was a significant reduction in amplitude A was seen in osteoporotic subjects compared to normal subjects. A significant negative correlation was also found between amplitude A and marrow fat content obtained from MR spectroscopy, indicating that fat content is an influential factor. Second, it appears that vascular permeability reduces as BMD decreases. Permeability may be influenced by factors such as capillary endothelial porosity, intrastitial or intraosseous pressure. How these physiology aspects interplay in osteoporosis should be the next step based on modeling study. The third main finding was a tendency for plasma elimination rate k_{el} to decrease as BMD reduced indicating that venous return also appears to reduce as BMD decreases.

Osteoporosis has an effect on marrow perfusion. Whether this effect is primary or secondary is unknown. This pilot study shows the potential for quantitative analysis of bone marrow perfusion by pharmacokinetic model that will in time increase our understanding of bone vascularity, metabolism and related diseases.

Acknowledgement: This work is supported by HK GRF grant CUHK464807.

References: [1] Mangiafico RA, et al, J Bone Miner Metab, 24:125-131(2006); [2] Griffith JF, et al, J Bone Miner Res, 23:1068-1075(2008); [3] Hoffmann U, et al, Magn Reson Med, 33:506-514(1995); [4] Lee JH, et al, Orthop Clin North Am, 40:249-257(2009).

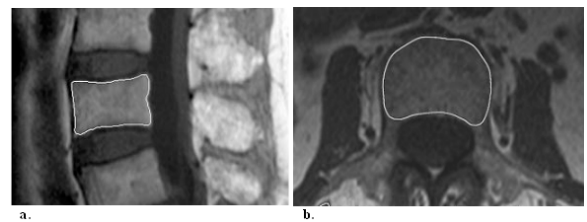


Fig.1. ROI drawn in T1-weighted MR image for male in sagittal plane (a) and for female in axial plane (b)

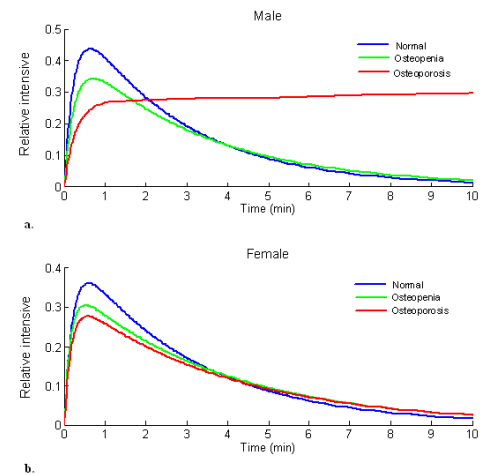


Fig.2. Simulation of representative DCE signal of groups with different BMD for male (a), and female (b), respectively.