Vertebra bone mineral density reduction is associated with vertebra blood perfusion reduction: dynamic contrast enhanced MRI study in a rat orchiectomy model

Y. X. Wang[1], H. Zhou[1,2], Y. F. Zhang[3], T. Kwok[3], D. K. Yeung[1], L. Qin[4], G. E. Antonio[1], and J. F. Griffith[1]

[1]Dept of Diagnostic Radiology and Organ Imaging, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China, People's Republic of, [2]Dept of Radiology, First Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang Province, China, People's Republic of, [3]Dept of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China, People's Republic of, [4]Dept of Orthopedics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China, People's Republic of

Introduction Recent clinical studies have shown that, both in male and female subjects, MRI derived blood perfusion parameters of vertebral marrow blood perfusion is significantly decreased in the osteoporotic subjects compared with those of the osteopenic subjects and normal bone density subjects (1,2). In the current study we set out to investigate whether it is possible to reproduce this clinical observations with dynamic contrast enhanced MRI in an osteoporosis model of male rat orchiectomy (ORX).

Materials and Methods: Eight 6-month old male Wistar-kyoto rats were used. These animals were housed 2-3 animal per stainless steel cage at 22°C temperature and with a 12-hr light and 12-hr dark cycle, and received a standard rat chow and water *ad libitum*. For MRI, studies were performed on a 1.5-T clinical whole-body imaging system (Philips Medical Systems) with a maximum gradient strength of 30 mT/m. Rats were anaesthetized, and the tail vein cannulated with a heparinised catheter. A surface coil (Micro 4.7, Philips Medical Systems) was put under the rat lumbar spine region as the radio frequency receiver and the body volume coil was used as the radio frequency transmitter. A sagittal plane through mid section of the lumbar spine was prescribed (Fig1). For dynamic scan, the MR parameters were as follow: short T1-weighted gradient echo sequence, TR=4 msec, TE=1.4 msec, flip angle 15, slice thickness= 5mm, average=1, matrix =128*51. MRI contrast agent was Gd-DOTA. A dose of 0.3mmol/kg (0.15 ml for a 250gram rat) was injected after initial baseline 60 dynamic image acquisition as quick bolus and followed by a flush of 0.5 ml normal saline. The total dynamic MRI duration was approximately 8 min and 800 dynamic images were acquired. Dynamic MRI images were processed in the radiologic workstation (Viewforum; Philips Medical System). Region of interest (ROI) was drawn over lumbar vertebra L3-L6 and the vertebra cortex was excluded in ROIs, the signal change over time was recorded (Fig 2). Maximum enhancement (ME), defined as the maximum percentage increase in signal intensity from baseline was derived from the first-pass phase of signal intensity enhancement [ME = [(SImax – SIbase)/ SIbase] x 100] (1,2). CT assessment of lumbar spine bone mineral density and MRI assessment of lumbar spine blood perfusion were performed at baseline prior to surgery and four weeks post ORX. The experimental protocol was approved by the local Animal Experiment Ethics Committee.

Results: Satisfactory CT and dynamic contrast enhanced MRI were obtained in all studied animals (Fig1, 2). After the pre-surgery CT and MRI study, one rat died due to an error of anesthetic agent overdose, leaving data of seven rats available at 4 weeks post ORX (table 1). CT measurement showed vertebra bone mineral density decreased by 16.6% at 4 weeks post-ORX (significant vs baseline, $p<0.05$, Wilcoxon signed ranks test). Dynamic contrast enhanced MRI showed maximum enhancement decreased by 17% at 4 weeks post-ORX (significant vs baseline, $p<0.05$, Wilcoxon signed ranks test).

Fig 1

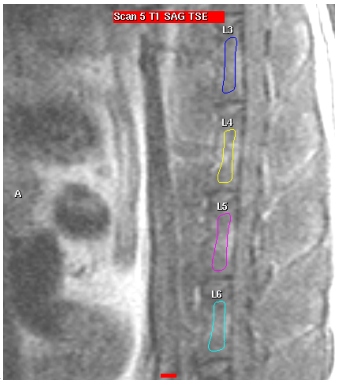

Fig 2

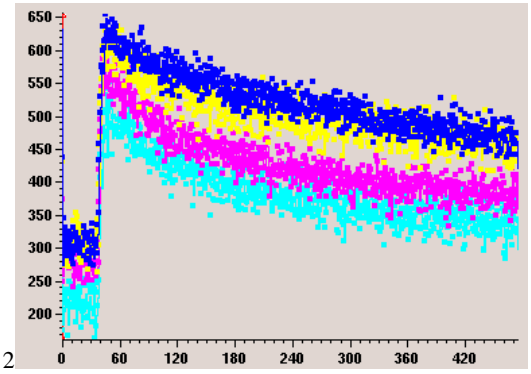

Fig 1, MRI sagittal view of lumbar spine of a rat. Four regions of interest have been drawn over lumbar vertebra bodies.

Fig 2, Dynamic MRI enhancement curve (signal intensity vs acquisition) of the same rat as in Fig 1. Curves of different colors indicate different ROIs. Similar enhancement is seen among the four vertebra bodies.

	baseline pre ORX (n=8)	4 weeks post ORX (n=7)
Bone mineral density (mean +/- SD, gram/cm^3)	1.135 (+/- 0.037)	0.946 (+/- 0.032)
MRI maximum enhancement (mean +/- SD, %)	151.7 (+/- 12.8)	125.9 (+/- 11.5)

Table 1 Rat lumbar vertebra bone mineral density and MRI maximum enhancement at baseline and post orchiectomy.

Discussion and Conclusion: Male osteoporosis is emerging as a central theme in bone research. As in females, hypogonadism or deprivation of gonadal hormones by surgical or chemical castration appear as principal risk factors in men that lead to bone loss and increased fracture incidence (3,4). Like ovariectomy (OVX), bilateral orchiectomy (ORX) in adult rats has been demonstrated as a useful model for studying rapidly progressing, high turnover bone loss and assessing the efficacy of antiresorptive therapies (5). To our knowledge, this is the first report to demonstrate that it is feasible to reproduce the clinical observation with dynamic contrast enhanced MRI that a decease of vertebra bone mineral density is associated with a decease of vertebra blood perfusion in the male rat osteoporosis model of ORX. That MRI can non-invasively detect blood flow changes of rat spine in vivo opens a new field for research. Further studies are being carried out in our laboratories to further validate our findings, including to use pharmacokinetic modeling to qualify blood flow and vessel permeability in the rat vertebra (6), and to observe pharmaceutical and diet intervention on rat spine bone mineral density and blood perfusion.

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