Potential Diagnostic Role of the MRI-Derived Internal Magnetic Field Gradient in Calcaneus Cancellous Bone for Evaluating Postmenopausal Osteoporosis at 3T

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Target audience: Translational researchers interested in noninvasive assessment of bone quality

Purpose: Even though bone mineral density (BMD) has been the accepted standard for osteoporosis diagnosis, BMD has a low predictive value on patients' risk for future fractures[1]. Thus, new approaches for examining patients at risk for developing osteoporosis would be desirable. Magnetic Resonance (MR) T_2^* measurements has been shown to yield quantitative information on trabecular-bone density as well as on bone micro-architecture[2,3]. T_2^* probes trabecular-bone microstructure by virtue of its sensitivity to magnetic susceptibility differences (ΔX) between bone and marrow[2]. Therefore, an increase in inter-trabecular space, which typically occurs in osteoporosis, prolongs marrow T_2^*[2,3]. A new potential surrogate marker for osteoporosis, the internal magnetic field gradient (IMFG), has recently been proposed[4,5]. In cancellous bone, the susceptibility mismatch between the solid matrix and interstitial liquid marrow generates internal gradients at the interface between bone and marrow. It has recently been shown that water IMFG measured in cancellous bone ex vivo is strongly associated with trabecular-bone density[5]. Furthermore, preliminary data obtained *in vivo* from the human calcaneus at 3T[5] indicate a progressive reduction of IMFG with age, suggesting IMFG to parallel the physiological reduction of trabecular-bone density.

Here, we assessed the potential of the effective IMFG to evaluate cancellous bone quality in the calcaneus of postmenopausal women. Toward this goal we examined the calcaneus of healthy, osteopenic and osteoporotic subjects at 3T, as classified by quantitative computed tomography (QCT) BMD, by measuring IMFG at various calcaneal sites and assessing associations between BMD and T_2^*.

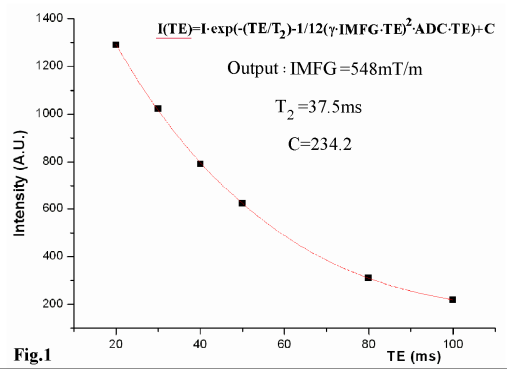

Fig.1

Methods: *Model:* The cancellous bone model used here is based on recent evidence from experiments both in vitro and in vivo[5] indicates that the water component in cancellous bone-marrow is prevalent in the boundary zone of the pores, while fat is mainly occupies the central intertrabecular space. An estimate of IMFG can be obtained from the spin-echo (SE) signal by quantifying the additional decay of the echo amplitude due to diffusion of water in local magnetic field gradients[5] (**Fig.1**). The local magnetic field gradient obtained in this manner is a function of temporal averaging governed by the water dynamics confined to the interface between fatty marrow and bone. *Imaging Protocol:* MR relaxometry and diffusion-weighted MR imaging (DWI) of the heel was performed in fifty-five women (mean age, 62.9±6.6 years) at 3T. The study protocol was approved by the local Ethics Committee. QCT of the L1-L3 vertebral segments was performed to classify the subjects into three groups according to BMD: healthy (n=8); osteopenic (n=25); and osteoporotic (n=22). A fat-suppressed multi-contrast spin-echo (MCSE) sequence (TR/TE=1500/20-30-40-50-80-100 ms; FOV=192x192 mm^2; matrix, 256x256; BW=130 Hz/pixel; NS=1, was used to obtain the SE decay from which the IMFG was extracted. To minimize the number of fitting parameters of the function:

$$S(TE) = S(0)\exp\left[-\left(\frac{TE}{T_2}\right) - \frac{1}{12}(\gamma \cdot IMFG \cdot TE)^2 \cdot ADC \cdot TE\right] + C$$

(where S(0) is the signal intensity at TE=0, T_2, is the spin-spin relaxation time), apparent diffusion coefficient (ADC) was evaluated from DWI images acquired in a single sagittal section of the calcaneus. A spin-echo segmented echo-planar imaging (EPI) sequence (TR/TE=1500/86 ms; FOV=192x192 mm^2; matrix, 128x128; BW=1954 Hz/pixel; epi factor, 7; diffusion sensitization along the anterior-posterior direction) at two different b-values (b=0 and 8000 sec/mm^2) was run (20). T_2^* was obtained with a FLASH sequence (TR/TE=1500/5-7-10-20 ms; flip angle, 30°; FOV=192x192 mm^2; matrix, 128x128; BW=260 Hz/pixel; NS=1). In all subjects, BMD T-scores, T_2^* and IMFG, were assessed in the whole calcaneus (CALCA) as well as in calcaneal subregions: subtalar (ST), tuber calcaneus (TC), and cavum calcaneus (CC). Between-group comparisons to assess group differences and Pearson correlation analysis were performed.

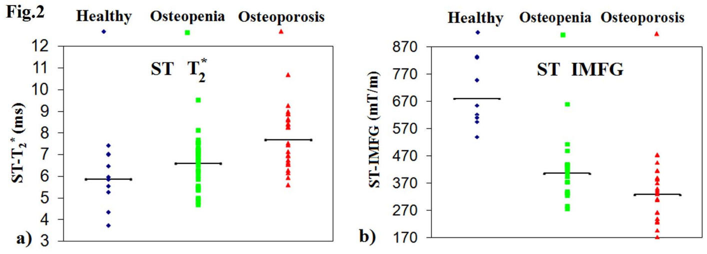

Table 1	1. Healthy (n = 8)	2. Osteopenic (n = 25)	3. Osteoporotic (n = 22)	*P* Value (1 vs 2)	*P* Value (2 vs 3)	*P* Value (1 vs 3)
CALCA-T_2^* (ms)	10.90 ± 1.51	12.78 ± 2.14	14.03 ± 2.63	*	ns	**
CALCA-G_i (mT/m)	486.2 ± 179.7	425.1 ± 147.3	333.8 ± 100.1	ns	*	**
ST-T_2^* (ms)	5.86 ± 0.90	6.66 ± 1.18	7.78 ± 1.21	ns	**	***
ST-G_i (mT/m)	623.07 ± 151.66	413.51 ± 93.05	325.17 ± 87.19	***	**	***

Data are mean ±SD; ns ($P \geq 0.05$); * ($P < 0.05$); ** ($P < 0.01$); *** ($P < 0.001$).

Results: An example of the fitting procedure used to compute IMFG from the SE decay as a function of time is displayed in **Fig. 1**. IMFG in the ST region was found to be greatest in healthy, intermediate in osteopenic, and lowest in osteoporotic subjects (**Table1**). IMFG values were significantly lower in osteopenics and more so in osteoporotics, paralleling T-scores for the ST region but not for all other regions examined (**Fig.2**). IMFG was significantly different between healthy and osteoporotic subjects in the TC, CC, and CALCA regions, but between osteopenics and osteoporotics for the CALCA region only. Similarly, T_2^* followed T-scores. However, group differences for this parameter were not significant for any of the regions examined. A moderate correlation (r= 0.635, p<0.01) was observed between IMFG and T-scores in the ST region but correlations were weaker for the remaining regions. T_2^* and T-scores correlated moderately (r=-0.514, p<0.01) in ST regions, but associations were weaker for the remaining regions.

Discussion: Our data suggests that IMFG measured in the calcaneus better discriminates healthy, osteopenic and osteoporotic women than does T_2^*, with the ST region being the strongest discriminator. This finding is in agreement with results obtained in a previous work[6] based on T_2^* measurements, where the ST region turned out to be the optimum calcaneal site for discriminating patients with vertebral deformities from those without such deformities. results shown here highlight the potential of IMFG measurement as an alternative approach to evaluate osteoporosis. Unlike T_2^* that results from coherence loss in the static dephasing regime caused by the induced inhomogeneous field, IMGF is a function of both ADC and static internal gradients. IMFG contains information on the trabecular network, which derives from the properties of the internal gradient (resulting from Δ□, between water and bone) averaged by the dynamics of the water confined to the narrow space between fat and bone surface. Therefore, IMFG is a function of the rate at which water molecules visit sites of different magnetic field.

Conclusion: BMD provides limited information on the two key properties that determine cancellous bone strength: bone's material composition and microstructural rearrangement. In contrast, IMFG reflects changes in both bone microarchitecture and composition that occur in osteoporosis. Our preliminary results suggest the ability of the IMFG evaluated in the ST region to discriminate healthy subjects from those with osteopenia and osteoporosis. Therefore, IMFG in the calcaneus obtained in large populations might allow establishment of a threshold on a single subject basis to determine whether intervention is indicated.

References: **1**.Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet 2002;359:1929-1936. **2**. Chung H, Wehrli FW, Williams JL, Kugelmass SD. Relationship between NMR transverse relaxation, trabecular bone architecture, and strength. Proc Natl Acad Sci USA 1993;90:10250-10254. **3**. Wehrli FW, Ford JC, Attie M, Kressel HY, Kaplan FS. Trabecular structure: preliminary application of MR interferometry. Radiology 1991;179:615-621. **4**. Sigmund EE, Cho H, Song Y-Q. High-resolution MRI of internal field diffusion-weighting in trabecular bone. NMR Biomed 2009;22:436-448. **5**. De Santis S, Rebuzzi M, Di Pietro G, Fasano F, Maraviglia B, Capuani S. In vitro and in vivo MR evaluation of internal gradient to assess trabecular bone density. Phys Med Biol 2010;55:5767-5785. **6**. Wehrli FW, Hilaire L, Fernández-Seara M, Gomberg BR, Song HK, Zemel B, Loh L, Snyder PJ. Quantitative magnetic resonance imaging in the calcaneus and femur of women with varying degrees of osteopenia and vertebral deformity status. J Bone Min Res 2002;17:2265-2273.