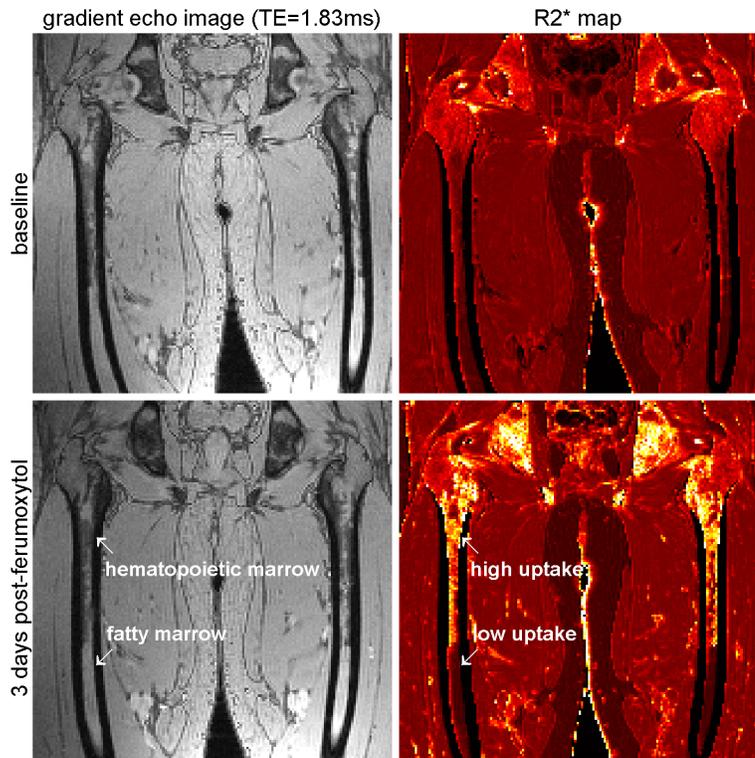


## Bone marrow uptake of ferumoxytol: a preliminary study in healthy human subjects

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**Introduction:** Ultrasmall superparamagnetic iron oxide (USPIO) particles are phagocytosed by macrophages, such as those in hematopoietic bone marrow, and have shown promise in improving the sensitivity and specificity of MRI for identifying marrow lesions [1,2]. Neoplasms and sterile inflammation, for example, exhibit minimal USPIO uptake [2-4], while osteomyelitis shows greater uptake [2,4]. In 2009, ferumoxytol (Feraheme, AMAG Pharmaceuticals) became the first USPIO agent to be approved for human use in the United States. It is indicated for the treatment of iron deficiency anemia, but can be used off-label as an MRI contrast agent. Experiments in rodents have shown that it produces persistent signal loss in hematopoietic marrow on T2\*-weighted images [5]. The purpose of this preliminary study was to investigate changes in marrow R2\* (= 1/T2\*) following ferumoxytol injection in healthy human subjects. Quantification of R2\* in marrow is complicated by the presence of fat, which renders the signal decay nonexponential. The lipid content, however, provides valuable complementary information about marrow composition, since it differs between hematopoietic and fatty marrow and among various pathological conditions. To maximize the accuracy of R2\* measurements and simultaneously quantify local fat content, complex-valued image data were acquired with a multiple gradient echo sequence and analyzed using spectral fitting.



**Fig. 1:** Images from the first echo (left) and corresponding R2\* maps (right) in a healthy 41-year old 80-kg man before and after ferumoxytol injection (top and bottom respectively). On the gradient echo images, hematopoietic marrow appears darker than fatty marrow, due to the relative phases of fat and water at TE = 1.83ms. The R2\* maps show dramatic responses to ferumoxytol in hematopoietic marrow and minimal increases in fatty marrow.

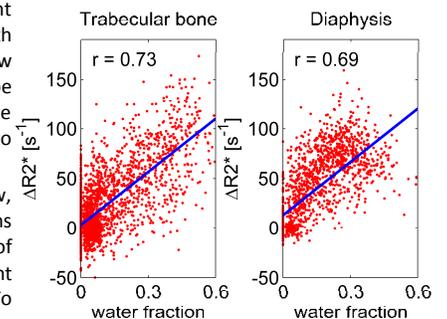
ferumoxytol, with an anatomical pattern that closely matches the distribution of hematopoietic marrow apparent on the gradient echo images (left). Figure 2 shows graphs of R2\* response versus water fraction in the same subject, where each point corresponds to a different voxel. Despite considerable scatter, high correlations are observed between R2\* response and water content, both in trabecular bone (left) and diaphyseal marrow (right), suggesting greater USPIO uptake in hematopoietic marrow than fatty marrow. Positive correlations were likewise observed in all the other subjects in whom R2\* could be evaluated. However, the correlations were significantly higher in trabecular bone ( $r = 0.78 \pm 0.08$ ) than in the diaphysis ( $r = 0.30 \pm 0.27$ ),  $p = 0.02$ . Inspection of the R2\* maps in cases of poor correlation revealed responses to ferumoxytol not only in regions of hematopoietic marrow, but also in certain areas with high fat content.

**Discussion:** This preliminary study demonstrates that ferumoxytol is efficiently taken up by normal bone marrow, with preferential absorption by hematopoietic marrow compared to fatty marrow. R2\* responses in certain regions of high fat content may indicate residual macrophage-rich stroma in converted marrow. The combination of ferumoxytol administration with a multiple gradient echo imaging technique that provides simultaneous assessment of R2\* and fat content may hold potential for increasing the specificity of MRI for differentiating marrow lesions. To explore this potential, further studies will be needed in patients with a variety of marrow pathologies.

**References:** [1] Metz S *et al.* *Eur Radiol* (2006) 16: 598–607, [2] Fukuda Y *et al.* *Eur Radiol* (2006) 16: 598–607, [3] Daldrup-Link HE *et al.* *Eur Radiol* (2002) 12:1557–1566, [4] Bierry G *et al.* *Eur Radiol* (2009) 19: 1604–1611 [5] Simon GH *et al.* *Acad Radiol.* Sep 2005;12(9):1190-1197, [6] Pai AB *et al.* *Clin Pharmacol Ther.* Aug 2010;88(2):237-242

**Methods:** Six healthy adults (4 men and 2 post-menopausal women, ages 22 – 57) were included in the study, and all provided informed consent to participate under an IRB-approved protocol. Among the exclusion criteria were pregnancy, a history of anaphylactic reaction and iron overload as determined by baseline T2\* imaging of the liver. The proximal femora were imaged in an oblique coronal plane at 1.5T (Avanto, Siemens) before and 3 days after intravenous ferumoxytol administration (5mg Fe/kg body weight). This interval was chosen since it corresponded to approximately five times the reported plasma half-life of the agent in humans [6], and was therefore expected to coincide with peak macrophage uptake. 3D imaging with 2.1mm isotropic resolution was performed using a multiple gradient echo sequence with monopolar readout gradients and 128 echoes, which were sufficient to permit calculation of a spectrum for each voxel. A short echo spacing of 1.83ms was chosen to prevent aliasing among the water and lipid peaks in the spectral domain. Other parameters included: minimum TE = 1.83ms; receiver BW = 1000Hz/pix; FOV = 400mm with base resolution = 192; 10 partitions with slice thickness = 2.1mm; TR = 255ms with FA = 25° to minimize T1 weighting. Images were reconstructed offline, and maps of fat, water and R2\* were generated by performing a pixel-by-pixel fit of the complex-valued image data as a function of echo time. The model used for the fitting procedure assumed a single relaxation rate R2\* for water and lipid components within the same voxel, and accounted for the multiple spectral peaks of fat by using the signal from subcutaneous fat as a reference, normalized by the area of the principal lipid peak. After coregistering baseline and post-contrast images using a 3D rigid-body transformation, R2\* changes were calculated for each voxel and correlated with the local water fraction, defined as (water signal)/(fat + water signals).

**Results:** No adverse reactions to ferumoxytol injection occurred. R2\* could be evaluated in all subjects except one (M25Y, 100kg), in whom post-contrast dephasing in hematopoietic marrow was too rapid to quantify with the 1.83ms echo spacing. Figure 1 shows results in a 41-year old man. The R2\* maps (right) demonstrate large responses to



**Fig. 2:** R2\* response versus water fraction for each voxel in trabecular bone (left) and the diaphysis (right) in the same subject as Fig. 1.