The Transport of Anionic and Nonionic MRI Contrast Agents into Human Hip Cartilage

E. Lammentausta[1], S. Lasic[2], D. Topgaard[2], O. Söderman[2], and L. E. Dahlberg[3]
[1]Department of Clinical Sciences, Malmö, Joint and Soft Tissue Unit, University of Lund, Malmö, Sweden, [2]Department of Physical Chemistry, University of Lund, Lund, Sweden, [3]Department of Orthopaedics, Malmö University Hospital, Malmö, Sweden

INTRODUCTION

Delayed gadolinium enhanced MRI of cartilage (dGEMRIC) is a quantitative MRI method utilizing anionic contrast agent Gd-DTPA^{2-}. The suggested mechanism is that the fixed charge density (FCD) of cartilage, induced by glycosaminoglycans (GAG), dictates the contrast agent distribution in cartilage via electrostatic repulsion [1]. The aim of the present study was to investigate the difference between transport of anionic and nonionic contrast agent into human hip cartilage.

METHODS

Two MRI contrast agents, namely anionic Gd-DTPA^{2-} (Magnevist, Bayer Schering Pharma AG, Berlin, Germany), and nonionic Gd-DTPA-BMA (Omniscan, GE Healthcare, Milwaukee, WI, USA) were used. Human femoral heads (n=8, age: 79±7, range 65-88) were harvested from patients undergoing hip replacement surgery due to hip fracture. The cartilage was visually intact. Two adjacent osteochondral plugs (diameter=4mm) were detached from weight-bearing region, one plug to be investigated using each contrast agent. A 200MHz (4.7T) spectrometer (Bruker Avance-II) was used to obtain profile images from the samples in depth-wise direction. First, T1 relaxation time was measured without contrast agent (inversion recovery sequence, TR=5 s, 16 TI's between 1 and 1000 ms, depth-wise resolution of 20 µm). Subsequently, the samples were exposed to 2mM solution of contrast agent. Due to test tube geometry the contrast agent could transport into the cartilage through cartilage surface only. After this, T1 was measured with 25 minutes intervals until ten hours.

The change in relaxation rate (ΔR1), reflecting the contrast agent concentration, was calculated for each time point, and the cartilage depth was normalized. Mean values of ΔR1 were calculated as a depth-wise profile after ten hours of contrast agent exposure, and as time-dependent curves at the most superficial, middle and deep cartilage (each ROI included 1/20 of total cartilage thickness). The difference between the ΔR1's was tested with Mann-Whitney U test for each time and depth.

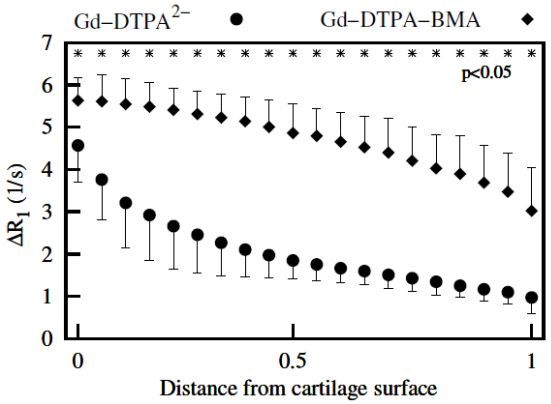

Figure 1. The change in relaxation rate representing the contrast agent concentration shown as a profile from cartilage surface to the deep cartilage after ten hours of transport through sample surface. The stars denote significant difference between Gd-DTPA^{2-} and Gd-DTPA-BMA

RESULTS

After ten hours of equilibration, the ΔR1 for Gd-DTPA-BMA was significantly higher than that for Gd-DTPA^{2-} at all depths (Figure 1). Both profiles displayed decreasing ΔR1 towards deep cartilage, but for Gd-DTPA^{2-} the depth-wise decrease was faster near the surface, whereas for Gd-DTPA-BMA it was faster in the deep cartilage.

For superficial cartilage, Gd-DTPA^{2-} reaches maximum concentration relatively fast, around two hours, whereas Gd-DTPA-BMA hasn't reached equilibrium in ten hours (Figure 2a). In the beginning, the concentration of Gd-DTPA^{2-} is higher, but eventually Gd-DTPA-BMA reaches higher concentrations with a significant difference from six hours onwards. For middle cartilage the concentrations are similar in the beginning, but Gd-DTPA-BMA reaches higher concentration (Figure 2b). Significant difference is displayed already after two hours. For deep cartilage, the situation is similar with lower concentrations and significant difference from three hours onwards (Figure 2c).

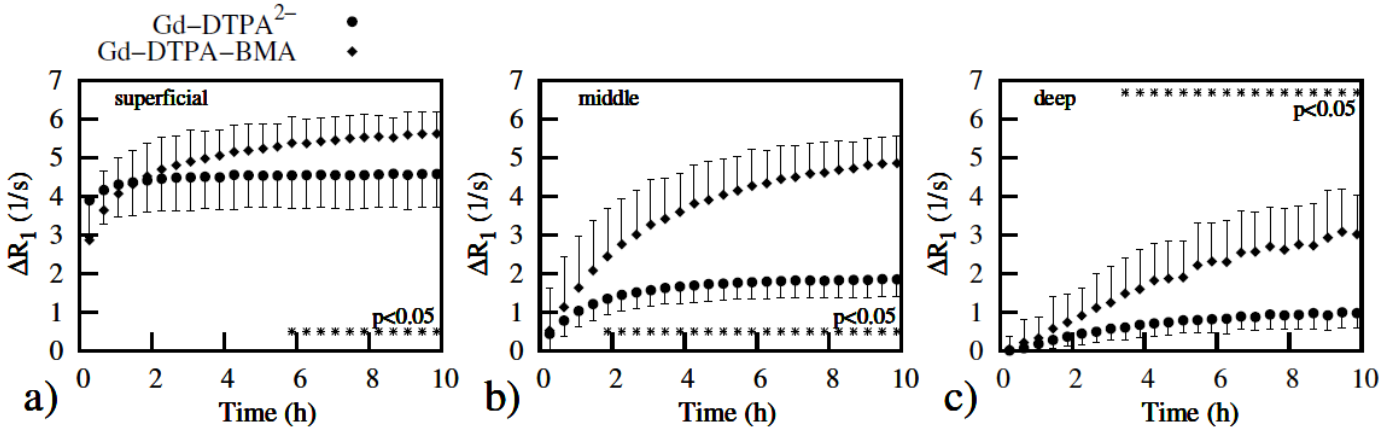

Figure 2. The time-dependent evolution of the change of the relaxation rate in cartilage at three different depths: a) superficial, b) middle and c) deep cartilage.

DISCUSSION

The concentration profiles after ten hours of equilibration are considerably different. The molecular weight of Gd-DTPA^{2-} is almost twice that of Gd-DTPA-BMA, so their diffusivity may affect the transport velocity. However, because the concentration of Gd-DTPA^{2-} reaches its maximum clearly sooner than that of Gd-DTPA-BMA, it is likely that the FCD of cartilage is limiting the amount of Gd-DTPA^{2-} in cartilage. Therefore we suggest that the concentration profile of Gd-DTPA^{2-} is limited by the FCD of cartilage and thus electrostatic repulsion, whereas the profile shape of Gd-DTPA-BMA is due to incomplete transport, even after ten hours of equilibration. This is supported by the rising Gd-DTPA-BMA concentration at all depths, the change being faster in the deep cartilage. After complete transport, the Gd-DTPA-BMA concentration is supposed to be constant everywhere. The present results are valid for in vitro studies. There are numerous other factors affecting contrast agent transport in vivo, for example clearance of the contrast agent and uncertainty of the concentration in synovial fluid after intravenous injection. Thus further studies are warranted.

REFERENCES

1. Bashir et al., Magn Reson Med 1999;41:857-865