Diffusion of manganese oxide nanoparticles into articular cartilage

Susanna Ahola[1], Ville-Veikko Telkki[1], Eveliina Lammentausta[2], Jessica M. Rosenholm[3], Elli-Noora Salo[2], Gamzegul M. Behrouz[1], Roberto Blanco Sequeiros[2,4], and Miika T. Nieminen[2,4]

[1]Department of Physics, University of Oulu, Oulu, Oulu, Finland, [2]Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland, [3]Centre of Functional Materials, Laboratory of Physical Chemistry, Åbo Akademi University, Turku, Finland, [4]Department of Radiology, University of Oulu, Oulu, Finland

TARGET AUDIENCE: Researchers with an interest towards degenerative joint diseases and paramagnetic non-ferrous nanoparticles with very high relaxivity.

PURPOSE: To investigate the feasibility of amorphous manganese oxide (MnOx) nanoparticles as contrast agents (CA) in articular cartilage. Due to their small size (nm scale), the MnOx nanoparticles are expected to diffuse faster into the cartilage tissue than current clinically used gadolinium-based CAs. Furthermore, the relaxivity (r) of the MnOx nanoparticles is very high [2] allowing a very low concentration to be used.

METHODS: The nanoparticles were produced according to a scheme presented in [1]. The diffusion of the MnOx CA into cartilage was followed by measuring T_1 relaxation maps. A 0.05 mM CA solution was allowed to diffuse into samples of bovine articular cartilage (through superficial cartilage only, Fig. 1A). The concentration of the CA was followed by measuring T_1 parameter images (Fig. 1B) first prior to injecting the CA solution (pre-contrast at 0 h) and then at repeated intervals until 24 hours of stabilization time (post-contrast 0-24 h). After 24 hours, the contrast agent solution was exchanged to pure phosphate buffered saline (PBS) in order to observe whether the contrast agent diffuses out from the tissue (wash-out 24-48 h). The T_1 relaxation maps were converted into concentration maps by observing the change in relaxation time and using the predetermined relaxivity of MnOx (Fig. 1C and equation within [3]) ($r = 15$ $(\text{mMs})^{-1}$ [2]). The T_1 parameter images were obtained at 7 T using a saturation recovery SE sequence (slice thickness 1 mm, FOV 8 mm x 10 mm, resolution 250 um x 78 um, TE=5 ms, TR = 44, 80, 160, 320, 640, 1280, 2560, 5120 ms). For comparison, the post-contrast part of the study was repeated also with a Gd-based contrast agent (Gd-DTPA). Change in contrast agent concentration was evaluated for superficial cartilage (SZ) and cartilage-bone interface (CZ, Fig. 1A)

RESULTS: The concentration of the both CAs in cartilage as a function of time is plotted in Fig. 1D. The figure shows that the CA nanoparticles diffuse very rapidly into the cartilage tissue, however they do not find a stable concentration in the more superficial cartilage within 24 hours. Instead, they continue to diffuse into the deep zone or calcified region (Fig. 1C). According to the T_1 (or concentration) maps the MnOx nanoparticles (or their dissociation products) are not removed from the deep- or calcified zone of the cartilage after 24 hours of equilibration with PBS.

DISCUSSION: The concentration of MnOx in deep tissue parts appears to grow higher than the actual concentration of the solution. It is possible that this apparent high concentration is due to the contrast agent being accumulated to the calcified region or due to accumulation of dissociated MnOx nanoparticles. Further studies are required to investigate the mechanism of CA accumulation and the actual location of accumulated CA.

CONCLUSION: MnOx penetrates articular cartilage tissue faster than a Gd-complex which is larger in size. MnOx nanoparticles or their dissociation products appear to bind to a region in the deep cartilage/calcified cartilage. MnOx complex could provide a marker for the assessment of calcified cartilage, typically with low signal due to short T_2 relaxation time.

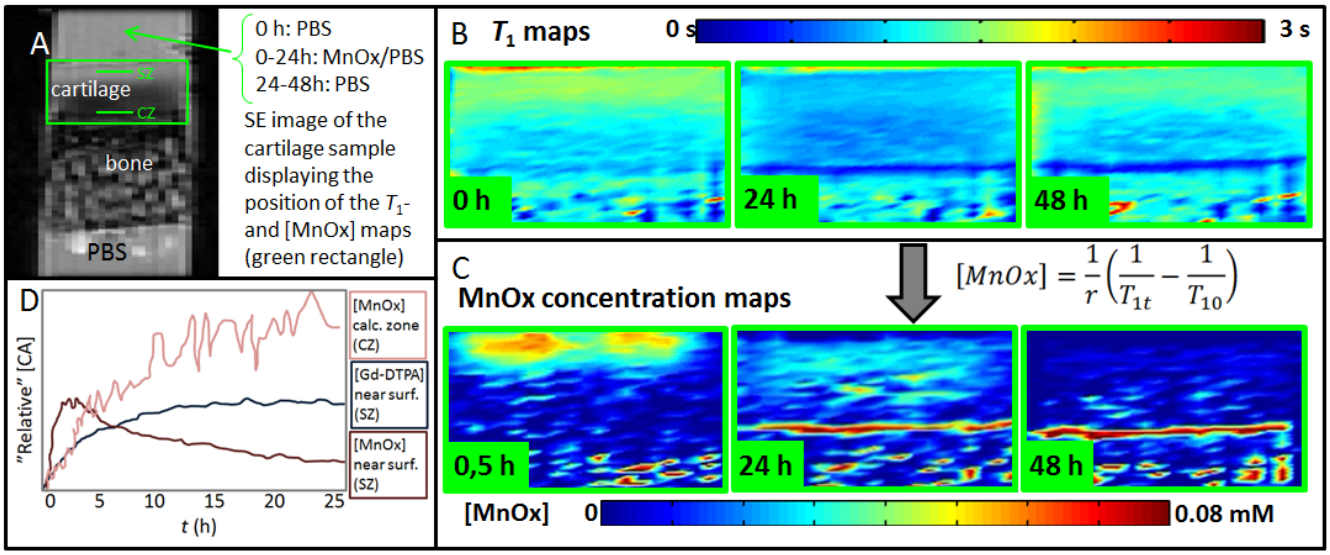

Figure 1. (A) SE image of articular cartilage sample. (B) T_1 maps from a selected area illustrated with green rectangle in (A). The first T_1 map is a pre-contrast map (0h), second (24h) is a post-contrast map measured 24h after inserting the CA and the third (48h) is a T_1 map 24 hours after exchanging the CA solution to pure PBS. (C) Corresponding CA maps. (D) Time evolution of CA concentration inside cartilage sample.

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