T1 of Cartilage with Gd-DTPA(2-) and GdHPDO3A: Implications for dGEMRIC Imaging

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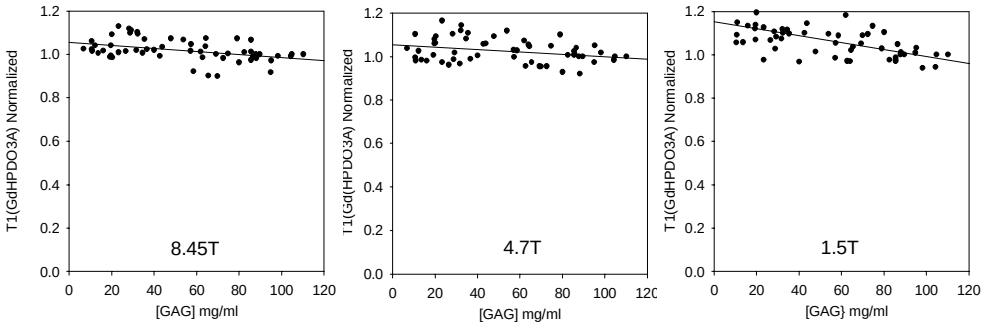
Introduction: dGEMRIC (delayed Gadolinium Enhanced MRI of Cartilage) is a technique for measuring the glycosaminoglycan (GAG) concentration in cartilage. It relies on the premise that the charged contrast agent $Gd(DTPA)^{2-}$ distributes in inverse relation to the negatively charged GAG molecules in cartilage. Thus, inasmuch as T1 in the presence of $Gd(DTPA)^{2-}$ is directly related to the $Gd(DTPA)^{2-}$ concentration, it will be related to the GAG concentration. This relationship assumes that T1 in the absence of contrast (T1o) and relaxivity (r) do not vary with tissue condition. However, recent studies have shown that the relaxivity of $Gd(DTPA)^{2-}$ is dependent on solid volume fraction at lower field strengths [1]. Another study demonstrated that the relaxivity of $Gd(DTPA)^{2-}$ changes with tissue degradation [2]. The latter study also demonstrated that the relaxivity of ProHance (GdHPDO3A), a nonionic contrast agent, tracks the relaxivity of $Gd(DTPA)^{2-}$ but distributes uniformly across normal and degraded cartilage. The goal of this study was to measure T1 in human cartilage tissue in the presence of GdHPDO3A for different levels of disease and at different field strengths. Since GdHPDO3A distributes uniformly in cartilage, the inference is that any variation of T1(GdHPDO3A) is due to T1o and relaxivity variation across the tissue, which can therefore be assessed.

Methods: Intact human knee cartilage-bone samples (n = 4) were obtained directly after total joint replacement surgery. Samples were first equilibrated in 1mM $Gd\text{-}DTPA^{2-}$ solution. T1 maps were obtained at three different field strengths, 8.45, 4.7 and 1.5 Tesla in order to assess the dGEMRIC index (T1(GdDPA)). After imaging $Gd\text{-}DTPA^{2-}$ was washed out and samples were equilibrated in 1mM GdHPDO3A and imaged again. ROIs (n = 57), consisting of at least 15 pixels, were chosen in cartilage and T1 was determined for those ROIs. ROIs were selected in such a manner that they corresponded to the same locations in each slice imaged under $Gd\text{-}DTPA^{2-}$ and GdHPDO3A at three different field strengths.

In order to determine how T1(HPDO3A) varies with tissue GAG depletion, GAG concentration was calculated from the dGEMRIC data at 8.45T. The conversion of T1(GdDTPA) to GAG at this field strength has been validated previously (3,4).

Results: The figure below shows T1(GdHPDO3A) for the 4 samples normalized to the highest GAG level of each sample, such that the percent variations at different field strengths could be compared. Note that at 8.45 Tesla there is little variation in T1(GdHPDO3A) across the sample, confirming the expectations from previous studies that GdHPDO3A distributes uniformly across tissue, and that there is little variation of T1o and Gd relaxivity for different tissue conditions at this field strength.



As the field strength decreases, T1(GdHPDO3A) increases slightly with GAG depletion. Since the distribution of GdHPDO3A is uniform across the sample, this implies that T1o and/or r varies across the sample. If these two parameters are assumed constant then the calculated concentration of GdHPDO3A would be underestimated for degraded cartilage (areas of low GAG) at lower fields. Therefore, one can infer that dGEMRIC similarly would underestimate the GdDTPA concentration at lower GAG levels, hence overestimating GAG in lower field studies.

Conclusions: Several comparisons between dGEMRIC and histology confirm the general correspondence between the dGEMRIC index and GAG concentration [3,4,5,6]. However, as further quantitation is desired, and as the quantitative studies go into the clinical studies at 1.5T, the effects of varying T1o and relaxivity need to be further investigated. The results show that in cartilage with fully depleted GAG an increase of approximately 3, 5 and 15% is observed in T1with GdHPDO3A at 8.45, 4.7 and 1.5T respectively. Thus these data would suggest that the relaxivity of the contrast agent is lower in cartilage that is devoid of GAGs when compared to almost healthy tissue (as relaxivity is expected to be more of a factor than T1o). This is consistent with a previous study [2]. The dGEMRIC technique assumes constant relaxivity of contrast agent in cartilage to predict the GAG distribution from the dGEMRIC index. If we take the relaxivity of contrast agent in healthy tissue as the quantitation parameter, then for completely degraded tissue dGEMRIC predicted GAG will be slightly higher then actual tissue GAG. At 1.5 Tesla, based on the changes observed in T1 of GDHPDO3A a decrease in GAG of 85% (from normal tissue) will be predicted as a decrease of 71%. Since the effect appears to be relatively monotonic with GAG concentration, relative GAG distribution can still be inferred, and the errors will be minimal for subtle lesions. Finally, the effects of in vivo temperature need to be considered, however the relatively constant T1(GdHPDO3A) in a previous clinical study [7] suggest that the effect under clinical conditions might be smaller than those shown here.

References: (1) Stanisz G & Henkelman M, Magn Reson Med 44:665-7, 2000; (2) Gillis A *et a*l.Magn Reson Med 48:1068-71, 2002. (3) Bashir et al Magn Reson Med 36:665-73, 1996; (4) Bashir A *et a*l. Magn Reson Med 41:857-65, 1999; (5) Nieminen et al, J Biomech, 2003. (6) Laurent et al, Magn Reson Med 50:541-49, 2003; (7) Bashir et al, Radiol 205:551-58, 1997.