Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) is superior to T1rho-mapping in measuring cartilage sulphated glycosaminoglycan content: preliminary results of an in-vivo validation study using an ex-vivo reference standard for cartilage sulphated glycosaminoglycan content

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Purpose: Quantitative radiological measures of cartilage composition have become of interest to non-invasively diagnose knee osteoarthritis (OA) or other cartilage diseases in an early stage, to follow subtle disease progression over time, and to assess the efficacy of potential novel treatment strategies for OA or other cartilage diseases. An example of such a technique is delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) which has become a standard for quantitative measurement of cartilage sulphated glycosaminoglycan (sGAG) content [1,2]. A drawback of dGEMRIC is the use of a contrast agent and the need for a long delay between contrast administration and acquisition of the MRI. T1rho-mapping has been proposed as non-contrast-enhanced alternative to dGEMRIC to also quantitatively measure cartilage sGAG content [3]. However, no thorough validation studies comparing both techniques acquired *in-vivo* against a tissue reference standard for sGAG have been performed. The aim of this study was to assess the correlation of *in-vivo* dGEMRIC and T1rho-mapping outcomes in osteoarthritis patients with cartilage sGAG content determined using an *ex-vivo* reference standard.

Methods: We analyzed data of 11 patients from an ongoing study in which knee OA patients (Kellgren and Lawrence grade 2-4) undergo T1rho-mapping and dGEMRIC at 3T before total knee replacement (TKR). All examinations were performed on a 3T MRI scanner (Discovery MR750, GE Healthcare, Milwaukee, USA) using a dedicated 8-channel knee coil. The imaging protocol for T1rho-mapping, which was acquired before contrast administration, consisted of a 3D fast spin-echo (FSE) sequence with T1rho preparation which has previously been published [4]. The spinlock frequency was 500 Hz and the spinlock times (TSL) were 1, 16, 32, 64 and 125 ms. The dGEMRIC protocol consisted of five 3D inversion recovery fast spoiled gradient-echo (IR-FSPGR) acquisitions with different inversion times (TI = 2100, 800, 400, 200 and 100 ms) [5] and was acquired 90 minutes after intravenous contrast administration (0.2 mmol/kg) [6]. In addition, a high resolution 3D spoiled gradient-echo (SPGR) sequence with fat suppression was acquired for segmentation of the cartilage regions of interest (ROIs) for the T1rho-mapping and dGEMRIC analyses. To correct for patient motion during acquisition of the 3D FSE and IR-FSPGR images, all acquired images were rigidly registered in 3D using the TSL=1 or TI=2100 images as fixed dataset and next, all FSE and IR-FSPGR images were registered to the high resolution SPGR dataset. Femoral and tibial regions were registered independently, using an automatic method based on maximization of mutual information [7]. T1- and T1rho-relaxation times were calculated in 6 cartilage regions (medial and lateral weight-bearing (WB) femoral condyles and tibial plateaus and non-WB cartilage of the condyles) which were manually segmented on the high resolution SPGR images (*figure 1*). Femoral and tibial cartilage was harvested during TKR and rescanned with contrast-enhanced microCT (CE-µCT), which served as reference standard for sGAG since it has been shown to accurately measure sGAG content [8]. We analyzed the correlation between T1- or T1rho-relaxation times and CE-µCT outcomes with linear regression.

Results: T1- and T1rho-relaxation times ranged between 280 – 834 ms and 31-48 ms respectively for dGEMRIC and T1rho-mapping. The outcomes of dGEMRIC had a strong negative correlation with CE-µCT in all tibiofemoral cartilage ROIs (r= -0.75; 95%CI= -0.85 – -0.59; r^2= 0.56) (*figure 2A*), while T1rho outcomes did not correlate with cartilage sGAG content in the same cartilage ROIs of the tibiofemoral joint (r= 0.00; 95%CI= -0.31 – 0.31; r^2= 0.00) (*figure 2B*). The correlation between dGEMRIC T1 relaxation times for the femoral (r= -0.81; 95%CI= -0.90 – -0.63; r^2= 0.65) and tibial (r= -0.68; 95%CI= -0.88 – -0.27; r^2= 0.46) cartilage analyzed separately was also good. For T1rho-mapping, there was also no correlation with outcomes of CE-µCT for the femoral (r= 0.03; 95%CI= -0.35 – 0.41; r^2= 0.00) and tibial (r= -0.09; 95%CI= -0.59 – 0.46; r^2= 0.01) cartilage if analyzed separately.
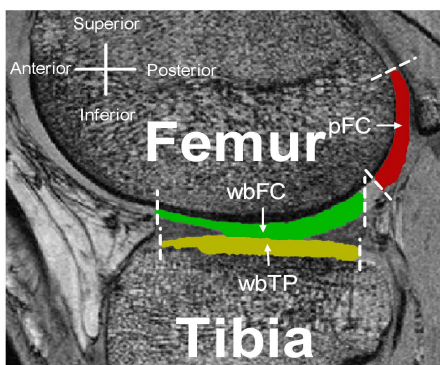

Figure 1: Cartilage regions of interest in which outcomes of dGEMRIC, T1rho-mapping and contrast-enhanced microCT were analyzed.
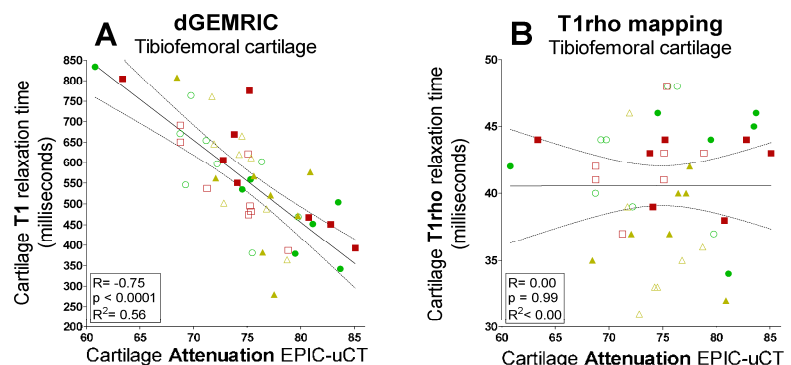
Figure 2: Correlation plot of outcomes of dGEMRIC and contrast-enhanced µCT (A) and outcomes of T1rho-mapping and contrast-enhanced µCT (B) in the tibiofemoral joint. Colored symbols represent cartilage ROI (*see figure 1*). Filled symbols: medial ROIs. Unfilled symbols: lateral ROIs.

Discussion: The preliminary results of the current study demonstrate that dGEMRIC T1 relaxation times have a strong correlation with cartilage sGAG content. For T1rho-mapping, no correlation between T1rho relaxation times and cartilage sGAG content was found. For dGEMRIC this is in agreement with previous *in-vitro* and one previous *in-vivo* study in which Watanabe et al correlated dGEMRIC outcomes with cartilage sGAG content measured using high-performance liquid chromatography [9]. Despite the strong correlation of dGEMRIC outcomes with sGAG content of cartilage measured using CE-µCT, the coefficient of determination is only moderate and therefore T1 relaxation times are likely to be also influenced by other composites of cartilage, e.g. collagen content or orientation, which was recently also suggested by other work [10]. For T1hro-mapping our result do not confirm earlier *in-vitro* reports suggesting that T1rho relaxation times represent sGAG content of cartilage due to mechanisms described previously [13]. However, our results are similar to two recent *in-vivo* studies in humans which also observed a weak correlation (r<0.45) between T1rho relaxation times and cartilage sGAG content measured using a DMMB assay of the lateral tibial cartilage [11,12]. As the complex T1rho relaxation mechanisms may be influenced by sGAG but also other composites of the cartilage [14], future research should further investigate the exact relationships between of T1rho relaxation mechanisms and biochemical composition of articular cartilage. This knowledge is of importance for the potential clinical application of T1rho-mapping as an outcome measure in research on OA or other cartilage diseases.

Conclusion: Our preliminary results suggest that dGEMRIC can accurately measure articular cartilage sGAG content, whereas T1rho-mapping is not suitable for this purpose. Therefore, despite the need to use a contrast agent, we consider dGEMRIC to be superior to T1rho-mapping for quantitatively measuring cartilage sGAG content.

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