IN VIVO COMPARISON OF INTRAVENOUS AND INTRA-ARTICULAR DGEMRIC AND DELAYED QUANTITATIVE CT ARTHROGRAPHY

Jukka Hirvasniemi[1], Katariina A.M Kulmala[2], Eveliina Lammentausta[3], Risto Ojala[4], Petri Lehenkari[5,6], Alaaeldin Kamel[3], Jukka S Jurvelin[2], Juha Töyräs[2,7], Miika T Nieminen[3,4], and Simo Saarakkala[1,3]

[1]*Department of Medical Technology, University of Oulu, Oulu, Finland,* [2]*Department of Applied Physics, University of Eastern Finland, Kuopio, Finland,* [3]*Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland,* [4]*Department of Diagnostic Radiology, University of Oulu, Oulu, Finland,* [5]*Department of Anatomy and Cell Biology, University of Oulu, Oulu, Finland,* [6]*Department of Surgery, Oulu University Hospital, Oulu, Finland,* [7]*Department of Clinical Neurophysiology, Kuopio University Hospital, Kuopio, Finland*

Target audience: Scientists and clinicians aiming to apply quantitative MRI techniques for assessing cartilage.

Purpose: Loss of glycosaminoglycan (GAG) side chains of proteoglycans is one of the earliest signs of degeneration of articular cartilage. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and contrast-enhanced CT, or delayed quantitative CT arthrography (dQCTA), were initially designed to probe GAG content of the cartilage[1,2]. These methods assume that negatively charged contrast agent distributes into cartilage in an inverse relation to GAG content of the cartilage[1]. Diffusion and distribution of contrast agent are influenced also by other factors, *e.g.*, water and collagen content[3]. Contrast-enhanced CT has not been thoroughly validated in the clinical setting. Furthermore, dGEMRIC and dQCTA have not been systematically compared *in vivo* in a knee joint of a same patient. Thus, the aim of the study was to compare dGEMRIC with intravenous ($dGEMRIC_{IV}$) and intra-articular contrast agent injection ($dGEMRIC_{IA}$) and dQCTA to each other.

Methods: Ten patients with knee pain were scanned at 3T MRI (Siemens Skyra, Siemens Healthcare, Germany) and using a clinical 64-slice CT (Discovery PET/CT 690, GE Medical Systems, USA). The study protocol was approved by the local ethics committee and informed consent was obtained from all subjects.

Prior to contrast agent injection in MRI, single-slice T_1 mapping was performed at the center of medial and lateral condyles using an IR-FSE sequence (TR/TE/TI=4060/8.6/50-3900 ms; FOV=120*120 mm^2, matrix=256*256; slice thickness=3 mm). Subsequently, 0.2 mM/kg of Gd-$DTPA^{2-}$ was injected intravenously and T_1 measurements were repeated after 90 minutes. Two weeks later, $dGEMRIC_{IA}$ was performed at 90 minutes after intra-articular injection of ioxaglate - Gd-$DTPA^{2-}$ mixture (see below). T_1 maps were generated using MATLAB (MathWorks inc., USA). Mean T_1 relaxation time (*i.e.*, dGEMRIC index) was separately calculated for $dGEMRIC_{IV}$ and $dGEMRIC_{IA}$ ($T_{1Gd,IV}$ and $T_{1Gd,IA}$, respectively) from the same regions as in dQCTA (medial and lateral trochlear grooves and condyles of femur and tibia). Change in relaxation rate was calculated for cartilage and synovial fluid ($\Delta R_{1,IV}$, $\Delta R_{1,IA}$, and $\Delta R_{1,SF}$) as follows: $\Delta R_1 = (1/T_{1Gd}-1/T_{1,0})$, where T_{1Gd} and $T_{1,0}$ are relaxation time values with and without Gd-$DTPA^{2-}$, respectively. Additionally, $\Delta R_{1,IA}$ was normalized by $\Delta R_{1,SF}$ ($=\Delta R_{1,IA}/\Delta R_{1,SF}$).

In CT (tube voltage=100 kV; tube current=160 mA, focal spot size=0.7 mm; pitch=0.53), ioxaglate - Gd-$DTPA^{2-}$ contrast agent mixture (20 ml; 105 mM Hexabrix 320, Guerbet, France and 2.5 mM Magnevist, Bayer HealthCare Pharmaceuticals, Germany) was injected intra-articularly. The knee joint was scanned at 5 and 45 minutes after the injection and mean X-ray attenuation values were measured from the same cartilage regions as in dGEMRIC and from synovial fluid. Cartilage parameters were normalized by the contrast agent concentration in synovial fluid ($=C_5/SF_5$, C_{45}/SF_{45}). Analyze 10.0 software (AnalyzeDirect, Inc., USA) was used for CT analyzes.

Either Pearson (r) or Spearman (r_s) correlation analysis (with 95% CI) was applied using SPSS 19 software (SPSS Inc., USA).

Results: T_1 relaxation time map of cartilage overlaid on top of a MR image and illustrative normalized X-ray attenuation map of cartilage overlaid on top of a CT image of a patient with cartilage lesion are presented in Figure 1. $dGEMRIC_{IV}$ showed the strongest correlation to normalized dQCTA parameters, while $dGEMRIC_{IA}$ correlated strongest with dQCTA at 45 minutes after the both parameters were normalized with contrast agent concentration in synovial fluid (Table 1). There was no relation between $dGEMRIC_{IV}$ and $dGEMRIC_{IA}$ when correlating either T_1 (r=-0.12 [-0.38–0.16], n=53, p=0.39) or ΔR_1 values (r_s=-0.01 [-0.29–0.27], n=50, p=0.95). When $\Delta R_{1,IA}$ was normalized by the $\Delta R_{1,SF}$, a significant correlation to $\Delta R_{1,IV}$ was established (r_s=0.52 [0.28–0.70], n=50, p<0.01).

Table 1. Spearman rank correlation coefficients (95% CI) between dGEMRIC and dQCTA parameters.

	C_5	C_{45}	C_5/SF_5	C_{45}/SF_{45}
$\Delta R_{1,IV}$	0.28 (-0.01–0.52)	0.39 (0.12–0.60)**	0.42 (0.16–0.63)**	0.72 (0.56–0.83)**
$\Delta R_{1,IA}$	0.42 (0.16–0.62)**	0.42 (0.17–0.62)**	0.27 (-0.01–0.50)	0.06 (-0.22–0.32)
$\Delta R_{1,IA}/\Delta R_{1,SF}$	0.10 (-0.18–0.36)	0.16 (-0.12–0.42)	0.13 (-0.15–0.39)	0.70 (0.53–0.82)**
$T_{1Gd,IV}$	-0.31 (-0.54–-0.04)*	-0.42 (-0.62–-0.16)**	-0.48 (-0.66–-0.23)**	-0.68 (-0.80–-0.50)**
$T_{1Gd,IA}$	-0.43 (-0.62–-0.18)**	-0.42 (-0.61–-0.18)**	-0.26 (-0.49–0.01)	0.03 (-0.24–0.29)

* $p < 0.05$, ** $p < 0.01$

C_x = cartilage, x = time in minutes from contrast agent injection, SF = synovial fluid, IV = intravenously administered contrast agent, IA = intra-articularly administered contrast agent.

Discussion: These results suggest that dQCTA is in best agreement with $dGEMRIC_{IV}$ at 45 minutes after ioxaglate injection. If judged only by visual evaluation, CT conducted at 5 minutes after the contrast agent injection had the best diagnostic quality for evaluation of cartilage lesions. $dGEMRIC_{IV}$ and $dGEMRIC_{IA}$ were related after the $\Delta R_{1,SF}$ was taken into account in $dGEMRIC_{IA}$ analyses. The results indicate the importance to take into account the contrast agent concentration in synovial fluid in dQCTA and dGEMRIC with intra-articular contrast agent injection. Normalization is justified because the contrast agent is diluted in synovial fluid and the volume of the synovial fluid in a joint varies among the patients. Limitations of the study include small sample size and the difference in time delay between contrast agent injection and imaging as well as differences in segmentation procedures in dGEMRIC and dQCTA.

Conclusion: $dGEMRIC_{IV}$ and normalized $dGEMRIC_{IA}$ correlated strongly with dQCTA. $dGEMRIC_{IV}$ and $dGEMRIC_{IA}$ were not correlated without taking into account the synovial fluid in $dGEMRIC_{IA}$. The findings of this study indicate the importance to normalize contrast agent concentration in cartilage with the contrast agent concentration in synovial fluid in dQCTA and dGEMRIC with intra-articular contrast agent injection.

References: 1. Bashir, Gray, Burstein. Gd-$DTPA^{2-}$ as a Measure of Cartilage Degradation Magn.Reson.Med. 1996;36:665-73. 2. Palmer, Guldberg, Levenston. Proc.Natl.Acad.Sci.U.S.A. 2006;103(51):19255-60. 3. Silvast, Kokkonen, Jurvelin, et al. Diffusion and near-equilibrium distribution of MRI and CT contrast agents in articular cartilage. 2009;54:6823-36.

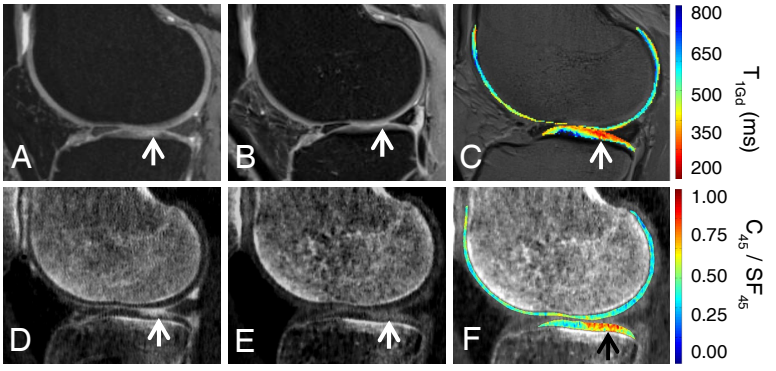

Figure 1. MR (**A**-**C**) and CT (**D**-**F**) images of a patient with cartilage lesion (arrow). (**A**) Anatomical DESS (TE/TR=5/14.1ms) and (**B**) IR-FSE images (TI/TE/TR=200/8.6/4060ms) without contrast agent. (**C**) T_1 relaxation time map of cartilage after intravenous contrast agent injection. (**D**) CT at 5 min and (**E**) CT at 45 min after injection. (**F**) Illustrative normalized X-ray attenuation map of cartilage at 45 minutes after injection (C_{45}/SF_{45}). Contrast of the images has been adjusted to enhance visibility of the lesion.