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Brief Report

Influence of delayed gadolinium enhanced MRI of cartilage (dGEMRIC) protocol on T2-mapping: is it possible to comprehensively assess knee cartilage composition in one post-contrast MR examination at 3 Tesla?

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SUMMARY

Objective: To evaluate the possibility of assessing knee cartilage with T2-mapping and delayed gadolinium enhanced magnetic resonance imaging (MRI) of cartilage (dGEMRIC) in one post-contrast MR examination at 3 Tesla (T).

Design: T2 mapping was performed in 10 healthy volunteers at baseline; directly after baseline; after 10 min of cycling; and after 90 min delay, and in 16 osteoarthritis patients before and after intravenous administration of a double dose gadolinium dimeglumine contrast agent, reflecting key dGEMRIC protocol elements. Differences in T2 relaxation times between each timepoint and baseline were calculated for 6 cartilage regions using paired *t* tests or Wilcoxon signed-rank tests and the smallest detectable change (SDC).

Results: After cycling, a significant change in T2 relaxation times was found in the lateral weight-bearing tibial plateau (+1.0 ms, $P = 0.04$). After 90 min delay, significant changes were found in the lateral weight-bearing femoral condyle (+1.2 ms, $P = 0.03$) and the lateral weight-bearing tibial plateau (+1.3 ms, $P = 0.01$). In these regions of interests (ROIs), absolute differences were small and lower than the corresponding SDCs. T2-mapping after contrast administration only showed statistically significantly lower T2 relaxation times in the medial posterior femoral condyle (−2.4 ms, $P < 0.001$) with a change exceeding the SDC.

Conclusion: Because dGEMRIC protocol elements resulted in only small differences in T2 relaxation times that were not consistent and lower than the SDC in the majority of regions, our results suggest that T2-mapping and dGEMRIC can be performed reliably in a single imaging session to assess cartilage biochemical composition in knee osteoarthritis (OA) at 3 T.

Introduction

Osteoarthritis (OA) is currently diagnosed based on clinical and radiographic criteria[1]. Unfortunately, conventional radiography, which visualizes cartilage indirectly, detects only late stages of degeneration. Novel magnetic resonance imaging (MRI) methods enable quantification of cartilage biochemical composition and microstructure. These quantitative MRI techniques are increasingly used in OA research, because they can detect early biochemical cartilage changes that precede morphological cartilage loss visible on conventional MRI[2]. The two most important cartilage components, glycosaminoglycans and collagen, can be determined with different quantitative MRI techniques. Because glycosaminoglycan content depletion and collagen integrity degradation occur at different stages of OA[3], quantification of both components is critical for comprehensive assessment of

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biochemical composition and structure of articular cartilage in early OA.

Two widely used and validated quantitative MRI techniques are delayed gadolinium enhanced MRI of cartilage (dGEMRIC) to measure proteoglycan content and T2-mapping to assess collagen network integrity[2]. Non-contrast alternatives for dGEMRIC are poorly correlated to glycosaminoglycan content (T1rho)[4] or require advanced MRI hardware (gagCEST and sodium MRI)[2]. A recent validation study showed a strong correlation of dGEMRIC with sulphated glycosaminoglycan content[4]. Thus, a combination of dGEMRIC and T2-mapping currently is an appropriate strategy for comprehensive assessment of biochemical composition of cartilage with MRI[5]. dGEMRIC requires intravenous administration of gadolinium dimeglumine (Gd-DTPA^{2-}) contrast agent, exercise to enhance contrast agent distribution, and a delay between contrast administration and image acquisition of 1–2 h[6]. As T2-mapping is acquired without any preparation, current practice is to acquire the techniques in separate MRI scan sessions pre- and post-contrast. Consequently, performing both techniques is costly, time-consuming, and difficult to implement in large clinical trials or clinical practice. Combining dGEMRIC and T2-mapping in a single scanning session would greatly improve the feasibility of comprehensive quantitative MRI assessment of cartilage, but requires knowledge of possible influences of dGEMRIC-specific protocol issues on T2 relaxation times. Therefore, we aimed at assessing the influence of different elements of our dGEMRIC protocol, i.e., contrast agent, cycling, and delay, on T2 relaxation time of knee cartilage. Our hypothesis was that dGEMRIC protocol elements do not influence T2 relaxation times and that dGEMRIC and T2-mapping can be performed in one scanning session.

Methods

Population

Two different groups of participants were used in this cross-sectional study. Approval from the Institutional Review Board of Erasmus MC (MEC 2014-096 and MEC-2012-218) and written informed consent was obtained from all participants. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000.

The influence of cycling and delay between hypothetical contrast administration and image acquisition was studied in 10 healthy volunteers without history of severe knee injury or specific knee disorder (5 males, mean age 24 years (SD (Standard Deviation) 2.1), average body mass index (BMI) of 23.5 kg/m^2 (SD 2.9)).

The influence of contrast agent was studied in 16 OA patients (6 males, 9 right knees) mean age 62.9 years (SD 6.4), average BMI 30.6 kg/m^2 (SD 5.0)) on the waiting list for total knee arthroplasty, recruited from the outpatient clinic of the Department of Orthopedic Surgery of Erasmus MC Rotterdam between October 2012 and December 2015. The inclusion criteria were radiographic knee OA (Kellgren–Lawrence grade[7] $\geq$1). Patients were excluded when they had renal insufficiency (glomerular filtration rate <60 mL/min), a history of previous reactions to MR contrast agent, or were physically unable to cycle. The medial knee compartment was most affected in 12 patients, the lateral compartment in the other 4.

MRI acquisition

All subjects were scanned on a 3 Tesla (T) MR system (Discovery MR750; GE Healthcare, Milwaukee, WI, USA) with a dedicated eight-channel transmit and receive knee coil (Invivo, Gainesville, FL, USA). T2-mapping was performed using a 3D fast spin echo (FSE) sequence with 5 echo times (3, 13, 27, 40, 68 ms); 3 mm slice thickness; and in-plane resolution of 0.5 $\times$ 0.8 mm[8]. Scan time was approximately 9:40 min. A 3D high-spatial-resolution fat-saturated fast spoiled gradient-echo (FSPGR) sequence was also acquired for cartilage segmentation (Appendix).

In the healthy volunteers, T2-mapping of the left knee was performed 4 times (Appendix). First, a baseline scan was made, followed by a second scan directly afterwards (without repositioning the subject); a third scan 70 min after baseline following 10 min of cycling; and a fourth scan 90 min after baseline. The second scan was used to determine the reproducibility of T2-mapping. Except for 10 min of cycling, the subjects did not load their knee during the total examination.

The participants with OA underwent our complete dGEMRIC protocol. This involves intravenous administration of 0.2 mmol/kg Gd-DTPA^{2-} (Magnevist; Bayer Schering, Berlin, Germany), 10 min of cycling at intermediate pace on an exercise bicycle, and a delay of 90 min, before image acquisition using a 3D inversion-recovery non-fat-saturated spoiled gradient-echo sequence with five different inversion times (Appendix)[4]. The baseline T2-mapping scan was performed 20 min before contrast administration. Post-contrast T2-mapping was done 60 min after contrast administration directly preceding dGEMRIC acquisition, reflecting the most efficient strategy when the two techniques are to be combined in a single imaging session without lengthening total examination time.

Image processing

Post-processing was performed using an in-house developed Matlab (R2011a; Math-Works, Natick, MA, USA) extension that incorporates automated rigid registration in 3D for motion compensation[9]. Full-thickness cartilage masks were manually segmented on 7 slices with 3 mm interval on the FSPGR sequence. Six cartilage regions of interest (ROI) were selected corresponding to the weight-bearing and posterior femoral condyles and tibial plateaus, both in the medial and lateral knee compartment. 'Weight-bearing' was defined as the cartilage within the outer perimeters of the menisci. The posterior ROIs consisted of the femoral cartilage behind the posterior meniscal horns. The acquired T2-mapping scans were registered to the FSPGR sequence to ensure exact matching of ROIs. Within each ROI, mean T2 was computed using a weighted averaging procedure[9].

Statistical analyses

Data was tested for normal distribution using the Shapiro–Wilk method. Paired *t* tests and Wilcoxon-Signed-rank tests were used for each cartilage ROI to compare T2 relaxation times made following the dGEMRIC protocol aspects with the baseline scans. A *P*-value < 0.05 was considered statistically significant. To assess the reproducibility of our T2-mapping MRI technique, we calculated the smallest detectable change (SDC), defined as the smallest amount of measurable change which cannot be attributable to measurement error. A change larger than the SDC exceeds the limits of agreement as defined by Bland and Altman. The formula for calculating the SDC is 1.96 $\times$ $\sqrt{2}$ $\times$ Standard Error of Measurement (SEM)[10]. The SEM needs to be calculated from a test-retest experiment in a stable population. It was derived from the first two measurements in the healthy population. The SEM was defined as the SD of the difference between the two scans divided by the square root of two ($SD_{difference}/\sqrt{2}$)[10]. All analyses were performed using SPSS 21.0 (IBM Corp, Armonk, NY, USA).