Detection of early cartilage damage

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Detection of early cartilage damage: feasibility and potential of gagCEST imaging at 7T

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Abstract

Objectives The purpose was to implement a fast 3D glycosaminoglycan Chemical Exchange Saturation Transfer (gagCEST) sequence at 7 T, test stability and reproducibility in cartilage in the knee in healthy volunteers, and evaluate clinical applicability in cartilage repair patients.

Methods Experiments were carried out on a 7-T scanner using a volume transmit coil and a 32-channel receiver wrap-around knee coil. The 3D gagCEST measurement had an acquisition time of 7 min. Signal stability and reproducibility of the GAG effect were assessed in eight healthy volunteers. Clinical applicability of the method was demonstrated in five patients before cartilage repair surgery.

Results Coefficient of variation of the gagCEST signal was 1.9%. The reproducibility of the GAG effect measurements was good in the medial condyle (ICC = 0.87) and excellent in the lateral condyle (ICC = 0.97). GAG effect measurements in healthy cartilage ranged from 2.6%-12.4% compared with 1.3%-5.1% in damaged cartilage. Difference in GAG measurement between healthy cartilage and damaged cartilage was significant (p < 0.05).

Conclusions A fast 3D gagCEST sequence was applied at 7 T for use in cartilage in the knee, acquired within a clinically feasible scan time of 7 min. We demonstrated that the method has high stability, reproducibility and clinical applicability.

Key Points
• gagCEST measurements are stable and reproducible
• A non-invasive GAG measurement with gagCEST can be acquired in 7 min
• gagCEST is able to discriminate between healthy and damaged cartilage

Keywords Cartilage • Glycosaminoglycans • Knee • Magnetic resonance imaging • Osteoarthritis

Abbreviations
CV Coefficient of variation
GAG Glycosaminoglycans
gagCEST Glycosaminoglycan chemical exchange saturation transfer
ICC Intraclass correlation coefficient
ICRS International Cartilage Repair Society
OA Osteoarthritis

Introduction

With the ageing of our society, the prevalence of degenerative diseases, such as osteoarthritis (OA), has increased [1]. OA is a degenerative whole-joint disease that affects the articular cartilage. Since cartilage tissue has a limited ability to regenerate, early identification of cartilage...
Numerical simulations

The 3D gagCEST sequence implemented in this work is a pseudo-steady-state pulsed 3D gradient echo CEST sequence recently developed in our group [22]. The sequence was optimised through the Bloch-McConnell simulations [23]. The following sequence parameters were investigated: the number of saturation pulses, transmit field (B1+) amplitude and duty cycle. All other sequence parameters were fixed to the values that were eventually used for data acquisition [22]. Gradient and RF spoiling was simulated by setting the transverse magnetisation components to zero. Two-pool (free water and GAG) Bloch-McConnell equations were solved numerically [24] assuming the parameters in Table 1. GAG effect size was quantified by the pool difference method:

\[
\text{GAG} = S(0.9 \text{ ppm}, M_A = 0) - S(0.9 \text{ ppm}, M_A = 1)
\]  

where \(S(\Delta \omega, M_A)\) is the simulated signal in the z-spectrum at \(\Delta \omega = 0.9 \text{ ppm}\), and \(M_A\) is the simulated amplitude of the GAG compartment. The saturation parameters were chosen to achieve an optimal GAG effect size, but with as low as possible acquisition time and within the limitations of the RF amplifier duty cycle.

MRI data acquisition

Eight healthy volunteers without a history of knee pain or trauma and five patients undergoing arthroscopy for repair of a focal knee cartilage defect were included in this study (approved by the medical ethics committee). Patients were selected within our specialised knee clinic of the University Medical Centre Utrecht. Patients undergoing an arthroscopy for cartilage repair on the femoral condyle were included for a pre-operative MRI. Exclusion criteria were as follows: history of cartilage repair, history of cruciate ligament tears or repair and/or trochlear/patellar cartilage damage. Informed consent was acquired from all the subjects after explaining the study procedures. MRI experiments were carried out on a 7.0-T whole-body scanner (Achieva; Philips Healthcare, Best, The Netherlands), using an in-house developed and built volume transmit coil and a dedicated 32-channel receiver wrap-around knee coil (MR Coils BV, Zaltbommel, The Netherlands).

The 3D gagCEST sequence included a pre-saturation module consisting of a train (\(n = 20\)) of sinc-shaped pulses (\(B_1 = 2 \mu\text{T}\), pulse length = 25 ms, duty cycle = 70%, based on simulations). The readout parameters were as follows: five-shot turbo field echo (TFE), TFE factor of 370, SENSE factor of 2, TR/TE/FA = 2.75 ms/1.4 ms/5 degrees, field of view = 140
The ICRS grade was graded in the femoral cartilage because we solely included patients with defects in the femoral condyles. The cartilage on the healthy condyle was graded with ICRS grade 0.

The reproducibility of the measurement of the GAG effect was assessed in eight healthy volunteers (mean age: 24 years, age range: 21 to 30 years, three males and five females). Each subject was scanned twice within the same scan session. The reproducibility of the measurement of the GAG effect was assessed in eight healthy volunteers (mean age: 24 years, age range: 21 to 30 years, three males and five females). Each subject was scanned twice within the same scan session.

The clinical applicability of the method was demonstrated by comparing the GAG effect size in healthy cartilage versus damaged cartilage in five patients before cartilage repair (age range: 21 to 41 years, all male, no significant/obvious varus or valgus leg axis). These patients were scanned up to 24 h prior to surgery. During surgery, cartilage defects were graded with the International Cartilage Repair Society (ICRS) grading scale (grade 0 to 4, 0 = no damage; 4 = full thickness cartilage defect) [25]. The ICRS grade was graded in the femoral cartilage because we solely included patients with defects in the cartilage of the femoral condyles. The cartilage on the healthy condyle was graded with ICRS grade 0.

### Image analysis

Data analysis was performed in MATLAB (R2016b, the MathWorks, Natick, MA, USA) with in-house developed processing scripts. The signal stability measurements were normalised with respect to the signal intensity of the first measurement. The signal stability was quantified from the averaged signal over all pixels in each of the three regions of interest (ROI): the medial condyle, the trochlear groove and the lateral condyle. These regions were also used for the quantification of the reproducibility of the GAG effect.

The reproducibility of the GAG effect size was assessed by means of Bland-Altman plots and correlation plots with corresponding intraclass correlation coefficients (ICC), i.e. the degree of absolute agreement among measurements (criterion-referenced reliability). To evaluate differences between healthy cartilage and damaged cartilage in the patients, a Wilcoxon signed rank test was applied.

### Results

### Simulation data

Figure 1 shows results of Bloch-McConnell simulations for the applied sequence. Twenty pulses were chosen as the number in the train, close to the maximum effect size for GAG but still within a clinically feasible acquisition time. A duty cycle of 70% was used to stay within RF amplifier duty cycle limits; 2 μT was chosen to approach the optimal effect size within the desired acquisition time. The combination of both leads to a maximum effect size of roughly 8 percent, which was in line with the chosen number of pulses in the pre-pulse train.
Stability and reproducibility

The coefficients of variation of the signal stability assessments are reported in Table 2. The average CV in the medial condyle was 2.00%, the average CV in the lateral condyle was 2.25%, and the average CV in the trochlea was 1.40%.

Figure 2 shows an example of a fitted CEST spectrum, with the GAG, water and MT pools visualised in purple, light blue and dark blue, respectively. The GAG effect can be observed at the expected offset around 0.9 ppm.

The correlation plots in Fig. 3 show strong reproducibility in the lateral condyle (ICC = 0.97, \( p < 0.01 \)) and the medial condyle (ICC = 0.87, \( p < 0.01 \)). The ICC for the trochlear groove was weak (0.064, \( p = 0.43 \)). Bland-Altman plots of the medial condyle and the lateral condyle are shown in Fig. 4. Bland-Altman analysis was not carried out in the trochlear groove because of the poor ICC. The Bland-Altman analyses show that there is no proportional bias between the two measurements.

Clinical applicability

A 3D segmented model of the knee cartilage of a patient is shown in Fig. 5. A difference in GAG effect in this patient was observed between the medial and the lateral sides. This specific patient had an ICRS grade IV defect in the medial condyle, which corresponds with the gagCEST findings. An arthroscopic view of this patient and the corresponding 3D gagCEST map is shown in Fig. 6. The ICRS grades and GAG effects of all patients are summarised in Table 3. The ICRS grade ranged from 3 to 4 (>50% thickness defects to full thickness cartilage defects). The GAG effect of healthy cartilage ranged from 2.6% to 12.4% and the GAG effect of damaged cartilage ranged from 1.3 to 5.1%. The GAG effect

![Fig. 1](image-url)  
(A) The simulated GAG effect size (%) as a function of the number of pulses in the CEST pre-pulse. (B) The simulated 3D plot of GAG effect size (%) as a function of the RF duty cycle (of the CEST pre-pulse) and \( B_{1+} \) field amplitude

### Table 2. Stability assessments of GAG effect at 0.9 ppm in healthy volunteers

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Gender</th>
<th>Scan</th>
<th>Medial CV (%)</th>
<th>Trochlea CV (%)</th>
<th>Lateral CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>F</td>
<td>1</td>
<td>1.61</td>
<td>0.88</td>
<td>1.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>1.67</td>
<td>2.07</td>
<td>1.11</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>M</td>
<td>1</td>
<td>0.89</td>
<td>0.52</td>
<td>2.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>1.25</td>
<td>0.52</td>
<td>0.73</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>M</td>
<td>1</td>
<td>3.2</td>
<td>1.96</td>
<td>1.74</td>
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<td></td>
<td></td>
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<td>2</td>
<td>5.44</td>
<td>2.96</td>
<td>3.34</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>F</td>
<td>1</td>
<td>1.64</td>
<td>1.55</td>
<td>6.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>1.54</td>
<td>0.57</td>
<td>0.88</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>F</td>
<td>1</td>
<td>1.08</td>
<td>1.54</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>1.67</td>
<td>1.38</td>
<td>3.54</td>
</tr>
</tbody>
</table>

Mean coefficient of variation: 2.00, 1.40, 2.25
in damaged cartilage was significantly different \((p < 0.05)\) from that in healthy cartilage.

**Discussion**

This study presents a fast 3D gagCEST sequence with full cartilage coverage, which can quantify the GAG effect in healthy volunteers and patients. The data were acquired within seven minutes and shown to be stable and reproducible. Moreover, the method could differentiate healthy from damaged cartilage in patients before their cartilage repair surgery.

The main goal of this study was to present a fast 3D gagCEST sequence. The acquisition time for the gagCEST sequence used in this study was 6 min 59 s, because a pseudo-steady state sequence was applied with an optimised number of saturation pulses. Other 3D sequences were published with scan times ranging from 11 min \[20\] to almost 15 min \[16\]. The latest study of the group of Trattnig reported a scan time of 19 min, albeit with better resolution compared with our study \[21\]. Note that a higher resolution reduces the signal to noise and is more prone to artefacts related to motion of the knee. All sequences published used the same or a comparable number of offsets and comparable field of view. We chose to implement an in-plane resolution of \(1 \times 1\) mm\(^2\) to minimise partial volume effects in the directions with the most curvature of the cartilage. This came with the drawback that the slice thickness needed to be 3 mm to achieve a sufficient SNR. Several other 3D gagCEST studies also implemented a comparable slice thickness of 3 mm \[15, 16\] or 5 mm \[28\]. An isotropic voxel size would be more ideal for 3D visualisation purposes, but this can only be achieved with a lower in-plane resolution or with much longer scan times.

This sequence was optimised using Bloch-McConnell simulations. Our goal was to minimise the scan time, which could lead to a sub-optimal CEST effect size. The number of pulses in the pre-pulse train could be increased to 60 for optimal effect size, as shown in Fig. 1A. However, this would increase
the shot time to 5.4 s, which increases the acquisition time per offset by 8 s. This increase of 20% in effect size (8% to 10%) would lead to a 40% increase in total scan time (6:59 to 9:54).

In our study we did not increase the scan time and selected a $B_1^+$ field amplitude of 2 $\mu$T and DC of 70% to obtain the maximum achievable effect size of 8%.

We applied a Lorentzian fitting algorithm for quantification of the GAG effect. We chose Lorentzian fitting to...
achieve better discrimination between the water peak and metabolite peak, in this case GAG. Because we expect GAG to resonate at 0.9 ppm [14], which is only 270 Hz upfield from the water peak, Lorentzian fitting was chosen. Lorentzian fitting also decreases the influence of $B_0$ inhomogeneities [29]. Previous literature used MTR asymmetry as a method for quantification, which is prone to these $B_0$ inhomogeneities [15, 16]. We used WASSR to correctly centre all CEST spectra as recommended by previous gagCEST studies [30].

The reproducibility in the lateral and medial femoral condyles was very good, which is promising for implementation in clinical practice. However, one should notice the poor reproducibility in the trochlear groove. The reproducibility in the trochlea was much lower compared to the condyles, which was also shown at 7 T in a study from Schreiner and colleagues [21]. The area around the trochlear groove is prone to movement of the patella. We speculate that this movement could be the cause of the poor reproducibility of the CEST spectra and their respective fits. Larger muscles could lead to more muscle twitches, ultimately leading to movement of the structures attached to the muscle, in this case the patella. The poor reproducibility could possibly be explained by this phenomenon. In addition, a 3-mm slice thickness could lead to volume averaging with surrounding tissue, especially in tissue with a high curvature such as the trochlea. Another limitation of this study is that measurements were only done on severe defects (ICRS grade III or IV) and healthy cartilage (ICRS grade 0). Because of the small population and the inclusion criteria for cartilage repair surgery in this study, no other defects were observed and gagCEST values of mild cartilage defects (ICRS grade I-II) are absent.

The GAG effect value varied across the included healthy volunteers and patients. The range of GAG effect values is rather large in patients, healthy cartilage ranging from 2.6% to 12.4%, compared with 1.3% to 5.1% for damaged cartilage. A similar range is observed in healthy volunteers (1.6% to 13.9%), which raises the question whether every volunteer had completely healthy cartilage. These ranges could indicate that there are underlying factors that affect the GAG effect, for instance age, gender or BMI, as has been suggested in other studies [31, 32]. Due to possible confounding effects of these factors, we chose not to compare the gagCEST values of patients with healthy volunteers.

Detection of the range of GAG effect values could be an interesting tool for osteoarthritis research, for monitoring of disease but also for earlier diagnosis. Therefore, a next step in this research would be an analysis of the GAG effect in patients with cartilage defects, ranging from small focal defects to osteoarthritic knees. This will reveal the value of gagCEST sequences in clinical practice and the patient characteristics affecting the GAG effect. In conclusion, this study presents a fast gagCEST sequence that is stable and reproducible and shows clinical value.

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### Compliance with ethical standards

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**Conflict of interest** The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

**Statistics and biometry** No complex statistical methods were necessary for this paper.

**Informed consent** Written informed consent was obtained from all subjects (patients) in this study.

**Ethical approval** Institutional Review Board approval was obtained.

### Methodology

- prospective
- diagnostic or prognostic study
- performed at one institution
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