Knee cartilage assessment with MRI (dGEMRIC) and subjective knee function in ACL injured copers: a cohort study with a 20 year follow-up

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SUMMARY

Objective: To assess knee cartilage quality and subjective knee function, 20 years after injury in anterior cruciate ligament (ACL) injured copers.

Method: We examined 32 knees using delayed gadolinium-enhanced magnetic resonance imaging (MRI) of cartilage (dGEMRIC), 20 years after a complete ACL tear. Only subjects who had coped with the ACL injury without ACL reconstruction (ACLR), and who presented without radiographic signs of osteoarthritis (OA) at an earlier 16-year follow-up, were included in this study. The quality of the central weight-bearing parts of the medial and lateral femoral cartilage was estimated with dGEMRIC (T1Gd). These results were compared with corresponding results in 24 healthy individuals, and with the subjects’ self-reported subjective knee function using the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire.

Results: The values of T1Gd in the medial and lateral femoral cartilage of the study group (mean (95% CI)), were 404 (385–423) and 427 (399–455) ms, not statistically different from those of the healthy reference group (P = 0.065 and 0.31). The subjective knee function 20 years after the injury, according to the five domains of the KOOS score, was good, with a mean score of 90 ± 11. Values of T1Gd for the medial femoral cartilage were correlated with the KOOS subgroup QOL (P = 0.021, Pearson correlation).

Conclusions: Subjects who have managed to cope with their ACL injury for 20 years with sustained good subjective knee function also seem to have knee cartilage of good quality, with T1Gd values not very different from a healthy reference group.

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Introduction

Osteoarthritis (OA) is the most common form of arthritis, and has enormous implications in terms of personal suffering and costs to society. According to the World Health Organization, OA is among the top ten conditions in the global burden of disease. The knee is one of the joints most frequently affected by OA. About 25% of individuals over 55 years of age have significant knee pain, and half of these show radiographic changes associated with OA. Risk factors for knee OA are clearly multifactorial. An anterior cruciate ligament (ACL) injury is one of the best documented risk factors for developing knee OA. ACL injuries are common among young athletes involved in sports requiring knee pivoting and cutting movements. It has been estimated that OA develops in about 50% of subjects with ACL tears 10–20 years after injury. According to the literature, meniscal injuries and meniscectomy are other well documented risk factors for the development of knee OA following ACL injury.

The gold standard in the diagnosis of OA is currently radiography. However, radiography is limited by insensitivity to early degenerative changes. Cartilage degeneration due to OA is not visible by radiography until decades after the onset of the disease, when the changes in cartilage are beyond repair. Furthermore, there is only a weak association between radiographic signs of knee OA and symptoms. There is evidence that new quantitative MRI techniques can be used to assess the loss of macromolecules such as glycosaminoglycans (GAGs) in cartilage during the early stages of OA. There are also indications that there is a better correlation between results obtained with these new quantitative MRI techniques and clinical outcomes.
techniques and symptoms, than between radiographic or routine MRI findings and symptoms\textsuperscript{20,21}. The depletion of GAGs from articular cartilage is one of the first observable effects of the OA disease process\textsuperscript{22}. GAGs are highly negatively charged sugar chains that are covalently bound to proteins, forming large aggregating proteoglycans\textsuperscript{23}. It has been shown that delayed gadolinium-enhanced magnetic resonance imaging (MRI) of cartilage (dGEMRIC) is a valid, reliable and non-invasive contrast-enhanced MRI technique that can be used to estimate the relative GAG content in articular cartilage in a clinical setting\textsuperscript{24}. A long relaxation time, T1Gd, is consistent with high cartilage GAG content. Results from dGEMRIC have already made valuable contributions to clinical research on early changes in the cartilage matrix. For example, it has been shown that it is able to discriminate between high and low cartilage quality in the knees of different groups of patients; lower cartilage quality being found in subjects with a lower level of physical activity following an ACL injury or a partial meniscectomy, and in those with a higher BMI or lower thigh muscle strength\textsuperscript{25}. In knees at risk of developing OA, dGEMRIC values at baseline have been shown to be predictive of radiographic signs of knee OA 6 years later\textsuperscript{26}. The aim of the present study was to evaluate knee cartilage quality 20 years after ACL injury, in a group of individuals who had not been treated with ACL reconstruction (ACLR) and in whom there was no radiographic evidence of overt OA, using dGEMRIC. This group of ACL copers was selected with the objective of determining whether the dGEMRIC method could be used to detect early changes in cartilage due to OA, before the cartilage degenerates too much to be repaired, as is the case when OA changes are visible on plain radiography. As ACLR changes the cartilage homeostasis, ACL reconstructed individuals were not included\textsuperscript{27}. We hypothesized that dGEMRIC would show inferior cartilage quality in this study subgroup, compared to that in healthy reference subjects, and that we would find an association between the subjects’ self-reported subjective knee function and the knee cartilage quality assessed using dGEMRIC.

Method

Subjects

One hundred consecutive patients referred to the Department of Orthopaedics, Lund, Skåne University Hospital, between February 1985 and April 1989 for acute ACL injury, were recruited to the study. Both short-term and long-term follow-ups were planned for this cohort, which was treated with early neuromuscular knee rehabilitation without primary ACLR. We have previously shown that these subjects had a favorable outcome 16 years after injury regarding functional performance and thigh muscle strength\textsuperscript{28}, subjective knee function\textsuperscript{29}, and knee laxity\textsuperscript{30}. The prevalence of tibiofemoral (TF) and/or patellofemoral (PF) OA was also low\textsuperscript{31,32}. Forty subjects from the 100 described above satisfied the following inclusion criteria for 20 year post-injury dGEMRIC imaging: NAACL and no radiographic OA (grade ≤ 1) 16 years post-injury (Fig. 1). Three subjects suffered from claustrophobia and could not complete the dGEMRIC examination. Four subjects declined to participate due to lack of time and logistic problems. One patient could not be contacted. The eight subjects who were not included did not differ from those included in the study group regarding patient characteristics, concomitant meniscal and chondral knee injuries or radiographic changes. Thus, 32 participants (M:F = 17:15, aged 35–61, mean 45 years) were examined with dGEMRIC and questionnaires (Fig. 1). The Local Ethics Committee approved the study, and written informed consent was obtained from all participants.

The dGEMRIC values obtained from the participants were compared with those in a healthy reference group described previously\textsuperscript{33}, comprising 24 individuals without any knee symptoms or previous knee injuries, examined with the same dGEMRIC protocol as that used in the present study. The individuals in the reference group were matched with the study participants regarding level of physical activity, and consisted of 14 men and 10 women with a mean age of 25 years and similar BMI to the group with acute ACL injury at inclusion (Table I).

![Fig. 1. Flowchart showing the inclusion of participants in the study.](image-url)
Inter-rater reliability (kappa statistic) was calculated for each ROI as input to a three-parameter model. The kappa statistic value of 0.52 for osteophytes. The maximum discrepancy in grading between the readers was 1. In such cases, the radiographs were re-read and consensus was reached.

Radiographic TF OA was considered present if any of the following criteria was fulfilled in any of the two TF compartments: JSN grade 2 or higher, the sum of the two marginal osteophyte scores from the same compartment ≥2, or grade 1 JSN in combination with grade 1 osteophyte in the same compartment. This definition approximates grade 2 knee OA based on the Kellgren and Lawrence scale.

MRI

Subjects were investigated with dGEMRIC 20.6 years (mean; range 18–23) after the injury, using a standard 1.5 T MRI system with a dedicated knee coil (Magnetom Vision; Siemens Medical Solutions, Erlangen, Germany). Initially, Gd-DTPA (Magnevist, Schering AG, Berlin, Germany) was injected at a dose of 0.3 mmol/kg body weight. To optimize the uptake of Gd-DTPA into the cartilage subjects exercised by walking up and down stairs for approximately 10 min, starting 5 min after injection. Postcontrast imaging of the cartilage was performed 2 h after the injection. Central parts of the weight-bearing lateral and medial femoral cartilage were identified, and quantitative relaxation time calculations were performed in a 3 mm thick sagittal slice on each condyle, using sets of six turbo inversion recovery images with different inversion times: TR = 2000 ms, TE = 15 ms, FoV 120 × 120 mm², matrix = 256 × 256, TI = 50, 100, 200, 400, 800 and 1600 ms. A full-thickness region of interest (ROI) in the cartilage was examined in the central parts of the medial and lateral femoral weight-bearing cartilage between the center of the tibial plateau and the rear insertion of the meniscus, as described previously. T1Gd was calculated using the mean signal intensity from each ROI as input to a three-parameter fit. dGEMRIC images were analyzed by one individual (HO) using the MATLAB-based Mokkula software developed by Eveliina Lammentausta, University of Kuopio, Finland. ROIs were drawn without any knowledge of pre-operative findings or surgical treatment. None of those examined had to be excluded due to motion artifacts in the MRI images (defined as having >12% of the ROI pixels above a T1Gd value of 1300 ms).

Table I
Characteristics of the study group, the healthy reference group and subjects not included in the present study

<table>
<thead>
<tr>
<th>Study sample at baseline (at injury) n = 32</th>
<th>Study sample at 20-year follow-up n = 32</th>
<th>Healthy reference group dGEMRIC n = 24</th>
<th>Subjects not included at baseline (at injury) n = 68</th>
<th>Subjects not included in 16-year follow-up n = 62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n</td>
<td>17 (53%)</td>
<td>14 (58%)</td>
<td>41 (60%)</td>
<td>38 (61%)</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>25 ± 6.4</td>
<td>25 ± 0</td>
<td>26 ± 8.0</td>
<td>42 ± 8.1</td>
</tr>
<tr>
<td>BMI, kg/m² (mean ± SD)</td>
<td>23.2 ± 3.1</td>
<td>22.5 ± 2.3</td>
<td>24.5 ± 2.6</td>
<td>26.8 ± 4.5</td>
</tr>
</tbody>
</table>

Self-reported knee function

The Knee Injury and Osteoarthritis Outcome Score (KOOS Swedish version LK 1.09, www.koos.nu) is a 42-item self-administered, knee-specific questionnaire based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)³⁰,⁴². KOOS comprises five subscales: pain, other symptoms, function in daily living (ADL), function in sport and recreation (sport/rec) and knee-related quality of life (QOL). A score from 0 to 100 is calculated for each subscale, 100 representing the best result. Subjects were instructed to complete the KOOS questionnaire by considering their injured knee at the time of dGEMRIC 20 years after injury. The KOOS has been found to be valid, reliable and responsive at follow-up after ACL injury and in subjects with knee OA⁴¹,⁴². KOOS results were compared to those of a population-based postal survey of random inhabitants in southern Sweden with a similar age range as the current cohort (n = 158, age 35–54 years, 51% women)³⁵.

The Tegnér score (range 0–10) was used to assess the individual’s level of physical activity at the time of dGEMRIC. Grade 10 represents highly demanding knee activities such as professional soccer or American football, and 0 represents no physical activity due to being on sick leave or having a disability pension. Grade 4 represents non-competitive activities such as jogging, bicycling and cross-country skiing.

Statistical analysis

P-values for comparisons of continuous data (T1Gd) were calculated using Student’s t test. T1Gd sub-analysis of individuals with or without meniscus surgery and of individuals with grade 0 or 1 OA changes were calculated using Student’s t test. The Pearson correlation was used to test for correlations between KOOS and dGEMRIC T1Gd values. No adjustment for age was made for T1Gd as dGEMRIC does not correlate with age. All tests were two-sided.
tailed, and \( P \leq 0.05 \) was considered to denote statistical significance. The statistical analysis was performed with SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). Results are given as the mean \( \pm 1\) SD (95% CI), unless otherwise stated.

**Results**

**dGEMRIC results**

The values of T1Gd in the group that had suffered an ACL injury were not significantly different from those in the healthy reference group, medially or laterally. The value of T1Gd medially in the injured group was 404 \( \pm 53 \) (385–423) ms vs 428 \( \pm 38 \) (412–444) ms in the reference group (\( P = 0.065 \)). The corresponding values laterally were 427 \( \pm 79 \) (399–453) vs 445 \( \pm 41 \) (428–462) ms (\( P = 0.31 \)) (Fig. 2).

No difference was observed in T1Gd obtained for the combination of medial and lateral femoral cartilage (bulk mean) in a subgroup analysis between subjects with radiographic signs of OA (grade 1 osteophyte or grade 1 JSN) and in subjects without osteophytes or JSN, values being 415 \( \pm 70 \) (380–450) ms and 412 \( \pm 38 \) (392–432) ms respectively (\( P = 0.85 \)). All subjects included in this study had a Kellgren and Lawrence grade \( \leq 1 \).

The values of T1Gd in medial femoral cartilage in subjects with (\( n = 3 \)) and without (\( n = 29 \)) a major medial meniscal injury (partial meniscectomy) were: 384 \( \pm 48 \) (329–439) ms and 407 \( \pm 53 \) (387–427) ms, respectively (\( P = 0.48 \)). The values in lateral femoral cartilage in subjects with (\( n = 10 \)) and without (\( n = 22 \)) a major lateral meniscal injury were: 410 \( \pm 105 \) (344–476) ms and 435 \( \pm 65 \) (407–463) ms, respectively (\( P = 0.41 \)). T1Gd was not related to BMI, the Tegnér activity score, age or sex (data not shown).

**Self-reported knee function**

The results obtained from the KOOS questionnaire for the study group, consisting of patients who had not undergone ACLR, were better than or similar to those obtained for the reference group\(^{13}\).

The scores obtained for the reference group were (mean \( \pm \) SD): pain 88 \( \pm 18 \), symptoms 88 \( \pm 16 \), ADL 89 \( \pm 19 \), sport/rec 78 \( \pm 29 \), and QOL 81 \( \pm 24 \). The corresponding scores for the study group (\( n = 32 \)) were: pain 95 \( \pm 10 \), symptoms 92 \( \pm 11 \), ADL 98 \( \pm 4 \), sport/rec 86 \( \pm 20 \), and QOL 81 \( \pm 20 \) (Fig. 3). The \( P \)-values obtained for the five subscales were: 0.034 (pain), 0.18 (symptoms), 0.0084 (ADL), 0.14 (sport/rec), and 1.0 (QOL).

KOOS increased with improving knee cartilage quality estimated with dGEMRIC, although the only association that was statistically significant was that between the QOL subscale and the quality of the medial femoral cartilage. Pearson correlations between the five KOOS subgroups and values of T1Gd obtained from the medial femoral cartilage were: \( P = 0.090 \) (pain), \( P = 0.17 \) (symptoms), \( P = 0.058 \) (ADL), \( P = 0.35 \) (sport/rec), and \( P = 0.021 \) (QOL). The corresponding Pearson correlations for the lateral femoral cartilage were: \( P = 0.72 \) (pain), \( P = 0.74 \) (symptoms), \( P = 0.90 \) (ADL), \( P = 0.19 \) (sport/rec), and \( P = 0.40 \) (QOL).

**Discussion**

This study of 32 subjects who had sustained an acute ACL injury, who were treated without ACLR and who showed no overt knee OA on radiography 16 years after injury did not show any statistically significant differences in knee cartilage T1Gd values (used as a measure of cartilage quality), 20 years after the ACL injury, compared to a healthy reference group. This group of ACL copers was selected with the objective of determining whether the dGEMRIC method could be used to detect early changes in cartilage due to OA, before the cartilage degenerates too much to be repaired, as is the case when OA changes are visible on plain radiography. We expected to find lower cartilage quality (i.e., lower T1Gd values) in the study group, and were surprised to find that the values did not differ significantly from those of a healthy reference group. We decided to compare T1Gd values with a healthy reference group which resembled the study group (age and activity level) just before the time of the ACL injury. An alternative would have been to compare T1Gd values with an age-adjusted study group without any previous knee injury but according to previous findings on the dGEMRIC method we believe that we then would have been required to include more individuals to discern any statistical significant difference between the groups.

Previously particularly low values of T1Gd have been observed in ACL injured subjects with a concomitant meniscus injury\(^{46}\). One reason for not finding a lower cartilage quality (i.e., lower T1Gd values) in the current study may be the small number of subjects (three) that had undergone medial meniscectomy, a well-known risk factor for the development of OA\(^{34,47–49}\). A second reason that might explain why these copers appear to have good knee cartilage quality 20 years after their ACL injury is the unique treatment they received in the original study\(^{50}\), where: all subjects were identified early after their knee injury; the individual pattern of knee injury was established and respected during the rehabilitation process; meniscus lesions were sparingly treated with meniscectomy; subjects were closely monitored, treated and educated by a competent physiotherapist to achieve functional knee stability, increased neuromuscular function and avoid giving-way of the knee; subjects initially (first year after injury) lowered their activity level. This treatment is different from how the acutely ACL injured patient is generally treated today, reflected in the previous study, in which the average follow-up time after ACL tear was 2 years and half of the study subjects were ACL reconstructed\(^{51}\). Although it’s hard to draw any solid conclusions from a comparison between this 20 year and a 2 year follow-up in two different cohorts, it is interesting to note that higher values of T1Gd were observed in this study. This may indicate that, if treated correctly, knee cartilage may have the ability to improve slowly over a period of several years after a severe knee injury. Thirdly, a selection bias could also to some extent explain why these copers appear to have good knee cartilage quality 20 years after their ACL injury as non copers that were subsequently ACL reconstructed (25%) were not included. Twenty
years after their ACL injury, the injured subjects in the present study had T1Gd values similar to those in a healthy reference group. This finding is in line with other aspects of knee function reported in previous studies on this cohort of well-functioning ACL-deficient copers. Moreover, the injured group was found to have better KOOS results than a randomly selected age-matched group. Longer follow-up of these individuals is needed to investigate development of knee OA in later years.

On a group level, higher or equal KOOS values were observed for the current cohort compared to the reference group, suggesting that the group as a whole seem to be in good content with their injured knee. On a subscale level, only an association between QOL and T1Gd was found. This is interesting as QOL together with sport/rec seems to be the most sensitive subscale with regards to ACL injury according to the Swedish ACL Register (www.aclregister.nu). All other subscales show results in line with numerous previous studies where the association between structural cartilage changes and symptoms has been weak.

Several studies have reported good agreement between cartilage GAG content and T1Gd values. A short T1Gd has also been reported to be a feature of early-stage knee and hip OA. However, we found no correlation between T1Gd and discrete radiographic knee changes (Fleming et al., Kellgren and Lawrence) in the present study. The primary objective of this study was not to investigate associations between radiography and the dGEMRIC method, but to determine whether dGEMRIC was able to detect changes in the cartilage in a cohort at risk of developing OA. Knee radiography was actually performed 4–5 years prior to the dGEMRIC investigation, but we nevertheless believe that the study group still had well-functioning knees, without overt OA with gross cartilage defects.

It may be argued that the study group was too small to allow any firm conclusions to be drawn. However, the results of previous studies performed by our group suggest that only a limited number of subjects is needed to detect statistically and clinically significant differences using dGEMRIC. This is mainly due to the low variability of the T1Gd values measured in the examined cohorts. Furthermore, it is not feasible to include the larger numbers of subjects required for multivariable modeling in dGEMRIC studies due to the high cost involved, the shortage of MRI capacity, and difficulties in scheduling subjects for examination. Between reference subjects (n = 24) and ACL injured subjects (n = 32), we only had a post hoc power of 82% and 36% to detect a difference of 24 ms medially and 18 ms laterally in T1Gd values from the femoral cartilage, with alpha set at 0.05. As the difference in T1Gd in previous studies has been approximately 50 ms the power a priori was close to 100% for the medial and lateral femoral cartilage. The actual T1Gd differences between the two groups were very small and would probably not be clinically relevant, even if observed in a larger cohort.

We examined the central weight-bearing cartilage of the medial and lateral femoral condyles because this is most commonly affected by early degenerative changes in cartilage. Others have argued that more information can be obtained by studying the whole volume of the knee cartilage, but we preferred to use the same MRI protocol as in our previous studies. Fleming et al. found similar T1Gd values in femoral and tibial cartilage in subjects who had sustained ACL injuries. This study, on a group of subjects that had sustained an ACL injury, and who were not treated with ACLR, shows that it is possible to maintain a good subjective knee function and good cartilage quality up to 20 years after injury. This is a very encouraging finding that may be important when counseling recently injured subjects who are prepared to abstain from pivoting sports, and who are willing to undergo neuromuscular knee rehabilitation without ACL surgery. In conclusion, our results show that subjects who have managed to cope with their ACL injury for 20 years, with good subjective knee function, also seem to have a good cartilage quality, as their T1Gd values were not very different from a healthy reference group.

Authors’ contribution

Paul Neuman: contributed to and critically commented on the design of the study; recruited patients to the study; collected and assembled data; analyzed and interpreted data; critically revised the article and wrote the manuscript.

Henrik Owman: contributed to conception and design; calculated dGEMRIC values; assembled and analyzed data; critically revised the article.

Gunilla Müller: commented on the study design; analyzed and interpreted data; provided technical MRI support and read the diagnostic MRI images; critically revised the article.

Martin Englund: contributed to and critically commented on the design of the study; collected and analyzed data from radiography; critically revised the article.

Carl Johan Tiderius: contributed to conception and design of the study; analyzed and interpreted data; critically revised the article.

Leif Dahlberg: contributed to conception and design of the study; analyzed and interpreted data; critically revised the article.

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Conflict of interest

The authors have no conflict of interest and this manuscript has not been submitted elsewhere.

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