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Osteoarthritis development related to cartilage quality-the prognostic value of dGEMRIC after anterior cruciate ligament injury

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SUMMARY

Objective: Rupture of the anterior cruciate ligament (ACL) increases the risk of developing osteoarthritis (OA). Delayed Gadolinium enhanced magnetic resonance imaging (MRI) of cartilage (dGEMRIC) investigates cartilage integrity through T1-analysis after intravenous contrast injection. A high dGEMRIC index represents good cartilage quality. The main purpose of this prospective cohort study was to investigate the prognostic value of the dGEMRIC index regarding future knee OA.

Method: 31 patients with ACL injury (mean age 27 ± 6.7 (±SD) years, 19 males) were examined after 2 years with 1.5T dGEMRIC of femoral cartilage. Re-examination 14 years post-injury included weight-bearing knee radiographs, Lysholm and Knee Osteoarthritis Outcome Score (KOOS).

Results: At the 14-year follow up radiographic OA (ROA) was present in 68% and OA symptoms (SOA) in 42% of the injured knees. The dGEMRIC index of the medial compartment was lower in knees that developed medial ROA, 325 ± 68 (ms±SD) vs 376 ± 47 (51 (7–94)) (difference of means (95% confidence interval (CI))), in patients that developed symptomatic OA (SOA), 327 ± 61 vs 399 ± 42 (52 (11–93)), and poor knee function 337 ± 54 vs 381 ± 52 (48 (7–89)) compared to those that did not develop ROA, SOA or poor function. The dGEMRIC index correlated negatively with the OARSI osteophyte score in medial ($r = -0.44$, $P = 0.01$) and lateral ($r = -0.38$, $P = 0.03$) compartments.

Conclusion: The associations between a low dGEMRIC index and future ROA, as well as SOA, are in agreement with previous studies and indicate that dGEMRIC has a prognostic value for future knee OA.

Introduction

The incidence of injury to the Anterior Cruciate Ligament (ACL) has been estimated at 0.81/1000 in ages 18–65 years[1], with the highest risk in younger active patients. Approximately 50% (15–84%) of ACL injured knees have radiographic osteoarthritis (ROA) in the femorotibial joint 10–20 years after the injury[2]. ACL reconstruction (ACLR) improves knee stability without decreasing the risk of developing ROA[2,3]. Young age at injury, in combination with a high risk of post-traumatic osteoarthritis (OA), implies that many patients will already suffer from OA in their 4th decade of life, an age where many treatment options, such as total joint replacement, are controversial.

OA development after ACL injury is multifactorial, involving mechanical factors and subsequent complex inflammatory responses depleting cartilage of glycosaminoglycan (GAG) and eventually disruption of the collagen II network[4]. At early stages of OA, the cartilage can still be macroscopically intact with changes undetectable by diagnostic tools such as radiographs, magnetic resonance imaging (MRI) and even arthroscopy.

Delayed Gadolinium enhanced MRI of cartilage (dGEMRIC) estimates the GAG content of hyaline cartilage by quantitative T1 analysis. After an intravenous injection, the negatively charged contrast medium distributes into the cartilage in an inverse relationship to the negatively charged GAG[5]. T1 within a cartilage region (the dGEMRIC index) is therefore a surrogate marker for cartilage quality. A low dGEMRIC index has been associated with an

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increased risk of developing ROA, both in the knee[6–8] and in the hip[9–12].

We have previously reported a low dGEMRIC index (indicating GAG loss) of the femoral knee cartilage in this cohort[13,14].

The aim of the present prospective study was to evaluate the prognostic value of the dGEMRIC index regarding future OA symptoms and ROA.

Methods

The cohort

The initial cohort included 40 patients with no previous knee injury who had sustained an acute ACL tear[13,14]. Patients were recruited from the orthopedic trauma center at Skåne University Hospital, Malmö, Sweden. Inclusion criteria were: age <40 years, closed physes and MRI verified ACL rupture in a previously uninjured knee. All patients were treated according to the standard treatment algorithm at the orthopedic department, which was not changed during the study period. The need for surgical ACL repair was based on the amount of persistent functional knee instability after physiotherapy.

Patients in the present study

For this 14-year follow-up study, all 40 patients from the original cohort were contacted with a letter of consent and patient-reported outcome measurements (PROMS). Despite multiple attempts, two patients never responded and three patients responded but never showed up for radiographs. Of the 35 patients that could be radiographically investigated, two had not completed the dGEMRIC investigation and two had invalid dGEMRIC investigations. Thus, 31 patients (19 men and 12 women) with complete dGEMRIC, radiographs and PROMS data were included, representing a 78% inclusion rate from the original cohort. There was no difference between participants and dropouts regarding sex, body mass index (BMI) or age.

21 of the 31 patients had been operated with ACLR and eight patients had been subject to partial meniscectomy. In one patient, operated with a high tibial valgus osteotomy 11 years after the injury, the immediate preoperative radiographs were used for radiographic scoring and the patient was dichotomized as symptomatic OA (SOA).

dGEMRIC

MRI was performed on a 1.5 T system with a dedicated knee coil (Magnetom Vision/Sonata; Siemens Medical Solutions, Erlangen, Germany). Gd-DTPA^{2-} (Magnevist®, Bayer Schering Pharma AG, Berlin, Germany) at 0.3 mmol/kg body weight was injected intravenously. Post-contrast MRI was performed 2 h after the injection. Regions of interest (ROIs) were drawn in the weight-bearing central parts of the lateral and medial femoral condyle cartilages according to a previously validated protocol[15]. Results are presented as mean T1 (ms) of each ROI (the dGEMRIC index). Average time from ACL injury to dGEMRIC for the 31 patients included was 2 years (median 24, range 7–61 months).

Radiography

Weight-bearing radiographs were taken according to a standardized knee OA protocol of standing antero-posterior radiographs with both knees in 20° of flexion. Using a validated method[16], radiographs were analyzed independently by two of the authors; an orthopedic surgeon specialized in joint replacement (J.T.) and a senior radiologist specialized in skeletal radiology (B.L.). In cases of discrepancy, the images were reassessed by the two investigators together and a consensus was reached. The OARSI atlas[17] was used for the medial and lateral compartments respectively, grading radiographic change on a four point scale for Joint Space Narrowing (JSN) (0–3, 0 = no evidence of JSN) and marginal osteophytes of femoral and tibial condyles (0–3 each, 0 = no bony change). Dichotomization for diagnosis of ROA was defined according to Englund *et al.*[16] as any of the following criteria fulfilled in either of the two femorotibial compartments: JSN grade ≥2, the sum of the marginal osteophyte score in the same compartment ≥2, or JSN grade 1 in combination with osteophyte grade 1 in the same compartment. This definition approximates grade two knee OA based on the Kellgren–Lawrence scale.

The sum of femoral and tibial marginal osteophytes in the OARSI score (grade 0–6) was used to quantify the grade of ROA in the medial and lateral compartments, respectively.

Patient reported outcome measures (PROMs)

The self-administered outcome scales Lysholm[18] and Knee Osteoarthritis Outcome Score (KOOS)[19] were sent to patients to complete and returned by mail. The KOOS data was used to define patients that had SOA according to Englund *et al.*[16]. In summary, this definition of SOA requires that the score for the KOOS subscale of knee-related quality of life *and* at least two of the four additional subscales should be below 86 after conversion to a 0–100 scale.

Similarly, a Lysholm score ≤84 reflects an unsatisfactory knee function and can be regarded as cut-off point for dichotomization to “poor function”[20].

Statistics

Tests for normal distribution, kurtosis and skewness were conducted. Continuous variables (e.g., the dGEMRIC index) are reported as mean values with standard deviation (mean ± SD), Student's *t*-test and 95% confidence interval (95% CI) was used to compare difference of means (MD). The following outcome variables were dichotomized and compared regarding the dGEMRIC index: ROA, SOA and poor knee function (Lysholm). Correlations were evaluated with Spearman rank correlation for ordinal variables (e.g., osteophyte score). Fisher exact test was used for dichotomous variables. Possible confounders (age, sex and BMI) were correlated (Spearman) with the dGEMRIC index. Logistic regression was used to calculate the predicted probability of ROA. A receiver operating characteristics (ROC) curve was used to illustrate the predictive value of the dGEMRIC index on an individual level. SPSS 25 was used for the statistical analysis.

Ethics

The study was approved by the Ethical Review Board at Lund University (Etikprövningsnämnden #EPN:2014/752, LU#73–96 and LU#651-00), the Radiation Protection Committee (Strålskyddskommittén #SSFo2014-050), and the Image Research Committee (BOF053). Patients signed a renewed informed consent before the 14-year follow-up data collection.

Results

Demographics

The median age at injury was 27 years (range 15–40) and at follow-up 40 years (range 26–53). Mean BMI had increased to 26.0 (SD 3.8) kg/m^2, (2.3 (95% CI 1.4–3.1)) from 23.7 (SD 2.7) kg/m^2 at

injury. Median follow-up time was 14 years (range 10.4–16.7) after injury and 12 years (range 9.7–13.6) after dGEMRIC. There were no significant correlations between dGEMRIC values and the possible confounding factors age ($r = -0.23$, $P = 0.92$), sex ($r = 0.07$, $P = 0.71$) or BMI ($r = -0.25$, $P = 0.18$).

Prevalence of OA

ROA was present in 21 of 31 (68%) of ACL-injured knees at follow-up. Of these, seven knees had isolated medial ROA, 11 had isolated lateral ROA and three knees had ROA in both compartments. ROA of the ACL-injured knee was present in 6 of 12 women and 15 of 19 men. OA symptoms (SOA) was present in 13 of 31 patients (42%). Two patients had SOA without radiographic signs of OA. BMI did not differ between patients with and without ROA, or SOA. A subgroup analysis of patients with and without ACL-reconstruction or meniscectomy was not considered reliable in this limited number of individuals.

dGEMRIC in relation to outcome

Knees that developed ROA in the medial compartment 14 years after injury already had a lower dGEMRIC index in the medial femoral cartilage 2 years after injury than knees with no ROA development. The mean difference between the groups was 50.7 ms (95% CI 7.2–94) (Fig. 1, Table I). Fig. 2 illustrates the calculated probability of developing medial compartment ROA. The medial dGEMRIC index (continuous variable) as a marker of medial radiographic OA (dichotomous variable) yielded an area under the ROC curve of 0.70 (95% CI 0.49–0.91) (Fig. 3). The best cut-off, maximizing the Youden index, was 330 ms with a sensitivity of 50% and a specificity of 91%.

In the lateral compartment, the difference between groups was 29 ms (95% CI −3.1–62) (Fig. 1, Table I). The grade of ROA, assessed with osteophyte score, correlated negatively with the dGEMRIC index, both in the medial compartment ($r = -0.44$, $P = 0.01$) and in the lateral compartment ($r = -0.38$, $P = 0.03$) (Fig. 4).

Patients with SOA at follow-up had a lower dGEMRIC index medially than patients without SOA (MD 52.4 (95% CI 11–93)) (Fig. 1, Table I). Patients with poor/fair knee function had lower dGEMRIC values in the medial compartment vs patients with good/excellent knee function at follow-up (MD 48.0 (95% CI 7.2–89)) (Fig. 1, Table I).

Discussion

Patients with an acute ACL-injury are suitable for the study of post-traumatic OA development since approximately half will have the disease within 10–15 years. The main result of the present study is very encouraging, i.e., that both clinical and ROA are associated with a low dGEMRIC index as soon as 2 years after the initial injury (Fig. 1). In addition, the dGEMRIC index had a negative correlation with the grade of ROA as assessed with the osteophyte score, suggesting a dose–response effect (Fig. 4). At an individual level, the dGEMRIC index has a limited predictive value, as illustrated by the large confidence interval in Fig. 2. The low dGEMRIC index in the cartilage of knees that eventually develop OA indicates a decreased GAG content in that cartilage, which in turn reflects impaired cartilage quality. GAG depletion is generally regarded as a very early event in the molecular pathway of OA progression[4]. There are clinical data to support the idea that GAGs can be replenished by intervention, such as physical exercise[21], osteotomy[9] and patella stabilizing surgery[22]. To determine the optimal treatment of an acute ACL-injury, whether this may be surgical or non-surgical, randomized controlled studies (RCT) are needed. One major issue with RCTs in OA is the long timespan needed for the ROA changes to occur. Instead, most researchers agree that we need early and sensitive markers for cartilage quality that ideally predict OA development.

Our results are in line with several previous dGEMRIC studies in other cohorts[6–12]. A low preoperative dGEMRIC index of hip cartilage was found to be the strongest predictor for a bad clinical outcome (OA progression) after periacetabular osteotomy in patients with hip dysplasia[9,12]. Similarly, a high preoperative dGEMRIC index before hip arthroscopy was correlated to a favorable clinical outcome 2 years postoperatively[11]. In hips with femoroacetabular impingement, baseline dGEMRIC predicted the ROA development at the 5-year follow up[10]. Regarding knee OA, Owman *et al.* have presented two different cohorts of middle-aged patients at risk of developing OA. In patients with early cartilage degeneration found at arthroscopy, a low dGEMRIC index was associated with ROA development 6 years later[8]. In patients who had been

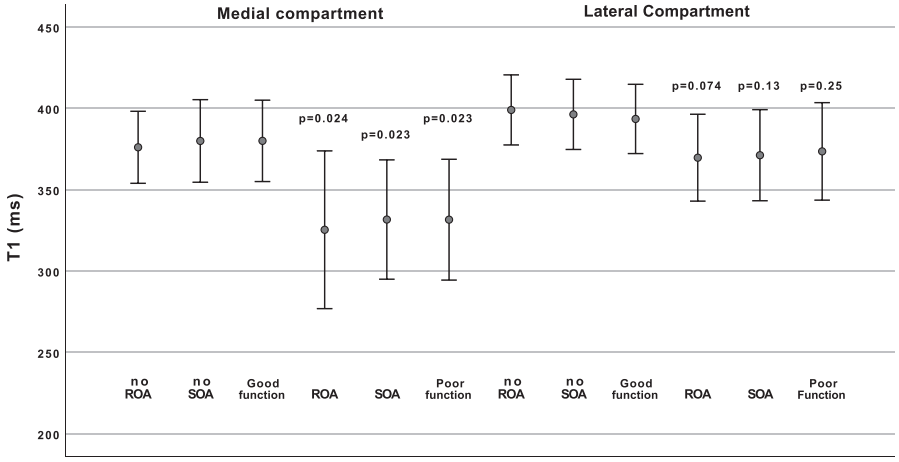

Fig. 1. The Delayed Gadolinium enhanced MRI of cartilage (dGEMRIC) index (ms) in medial and lateral femoral cartilage 2 years after anterior cruciate ligament (ACL) injury related to radiographic OA (ROA) and symptomatic OA (SOA) at the 14-year follow-up. Knees that developed ROA, SOA or poor knee function (see methods for details) had lower dGEMRIC index medially than knees that did not. "•" represents mean value with 95% CI as error bars. Difference of means and absolute values are presented in Table I.

Table I
The Delayed Gadolinium enhanced MRI of cartilage (dGEMRIC) index (**bold**) 2 years after anterior cruciate ligament (ACL) injury related to ipsicompartmental radiographic OA (**ROA**, Yes/No), OA symptoms of the whole knee (**SOA**, Yes/No) and knee function (**Lysholm <84**, poor/good) 14 years after the ACL injury. Results are presented for medial and lateral femoral cartilage in separate columns

Outcome in respective compartment	ROA medial	ROA lateral	SOA medial	SOA lateral	Lysholm <84 medial	Lysholm <84 lateral
Yes						
mean (±SD) T1 ms	**325**(68)	**370**(46)	**332**(61)	**371**(46)	**333**(59)	**375**(45)
n=	*10*	*14*	*13*	*13*	*14*	*14*
No						
mean (±SD) T1 ms	**376**(47)	**399**(42)	**380**(51)	**396**(43)	**381**(52)	**394**(46)
n=	*21*	*17*	*18*	*18*	*17*	*17*
Student *t*-test	*.024*	*.074*	*.023*	*.13*	*.023*	*.25*
p=						
difference of means	50.7	29.3	52.4	25.1	48.0	19.2
95% CI	7.2–94	−3.1–62	11–93	−8.1–58	7.2–89	−14–53

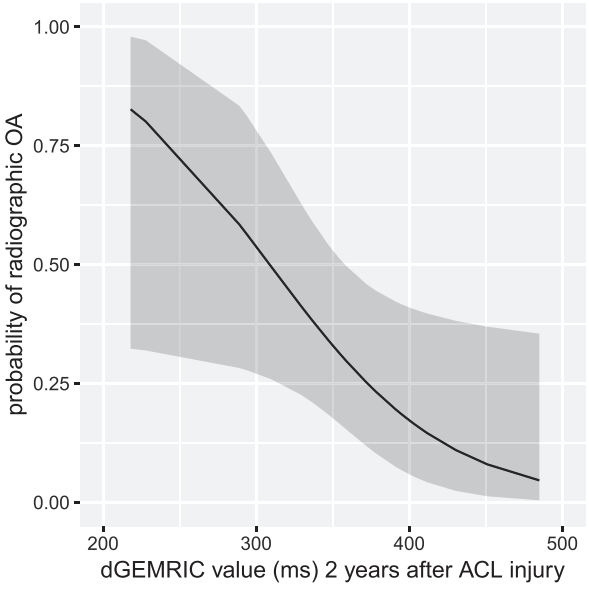

Fig. 2. dGEMRIC index of medial femoral cartilage vs calculated probability of medial ROA at the 14-year follow-up, the shaded area represents 95% CI.

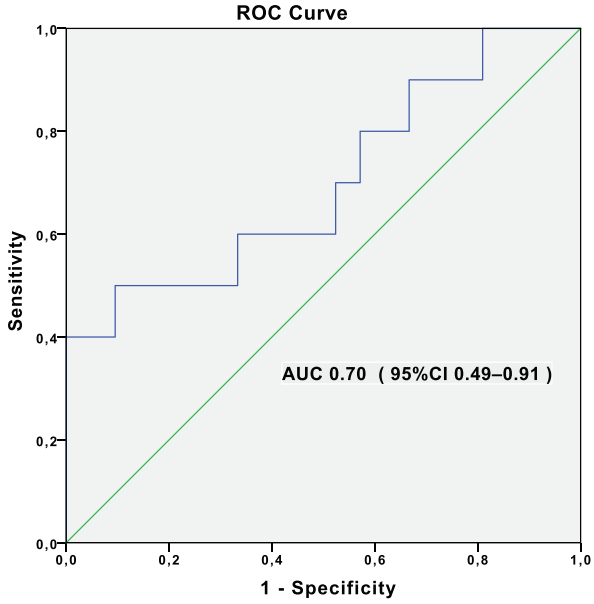

Fig. 3. ROC curve of medial dGEMRIC index as a marker of ROA outcome. The area under the curve was 0.70 (95% CI 0.49–0.91). The maximal Youden index was at 330 ms with a sensitivity of 50% and a specificity of 91%.

operated with a partial medial meniscectomy, the dGEMRIC index correlated negatively with the amount of ROA 11 years later[6]. More recently, we have shown a negative correlation between the dGEMRIC index in the adjacent cartilage after surgical cartilage repair and future OA, again suggesting a clinical relevance of dGEMRIC[7].

There are issues with the dGEMRIC technique in addition to the inherent complexity with intravenous contrast injection 1–2 h before imaging. Emerging safety concerns have restricted[23,24] the use of Gd-DTPA^{2-} since the contrast agent has been associated with both nephrogenic systemic fibrosis (NSF) in patients with severe renal impairment[25], and accumulation in the brain after repeat investigations[26]. Such concerns limit the future use of Gd-DTPA^{2-} for *in vivo* application. However, macrocyclic gadolinium chelates of higher molecular stability, such as gadoteric acid (Gd-DOTA^{1-})[27] have been tried as substitution for Gd-DTPA^{2-} in dGEMRIC of hip, wrist and knee cartilage with comparable results[28]. Ultimately, national authorities must determine which contrast agents can be safely used in patients as well as in healthy subjects.

Much research has also been focused on MRI techniques that do not require contrast enhancement, such as T2-mapping, gagCEST[29], Ultrashort echo-time T2* (UTE-T2*)[30] and sodium MRI[31]. For example, data from the Osteoarthritis Initiative cohort has shown that long T2 values of tibiofemoral cartilage may predict ROA over a 4-year period[32]. In a recent study of patients 2 years after ACLR, UTE-T2* profiles from both the reconstructed and the contralateral knees differed from that of uninjured controls[33].

In the present study we found a high rate of ROA (68%) 14 years after an acute ACL injury. A direct comparison of our results with other studies is hampered by many factors, such as different criteria for OA diagnosis, age at injury, duration of follow-up, gender, mechanism of injury, treatment, rate of loss to follow-up, etcetera. The heterogeneity of these factors is illustrated by the fact that reported rates of ROA after ACL injury varies between 10% and 90% with an average of 50% after 10–20 years[2]. The subjects in our study represent a cross sectional selection as they were prospectively and consecutively recruited from the ER department of one single hospital.

The main limitation of our study is the small number of patients, which disenables a multivariate analysis. It is also important to point out that the clinical course of each patient varies considerably, despite the strict inclusion criteria. Some patients need ACLR and some become subject to additional meniscus surgery. From the present data, we cannot evaluate the impact of those individual variables. Considering such and other patient related factors, the

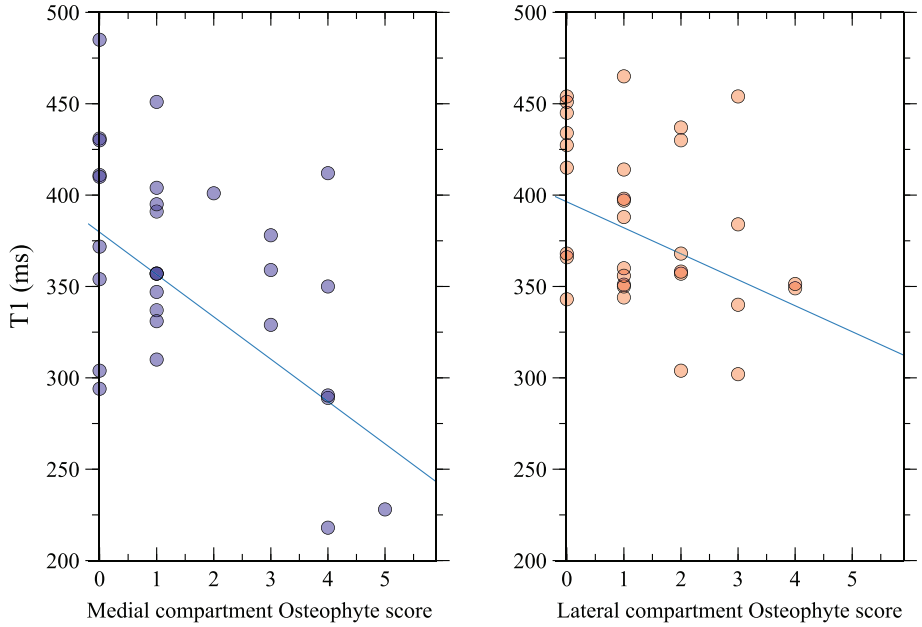

Fig. 4. There was a negative correlation between the dGEMRIC index 2 years after injury and grade of OA, assessed with the OARSI osteophyte score, 14 years after injury (medial compartment $r = -0.44$ ($P = 0.01$, $n = 31$), lateral compartment $r = -0.38$ ($P = 0.03$, $n = 31$)).

prognostic level of the dGEMRIC index on an individual level may be limited. Despite these limitations it is intriguing that the cartilage quality, represented by the dGEMRIC index, seems to influence the long-term outcome after ACL-injury.

In summary, the associations between a low dGEMRIC index and future ROA, as well as SOA, are in agreement with previous studies and indicate that dGEMRIC has a prognostic value for future knee OA.

Author contributions

JT: Study initiation and design, recruitment of patients, radiographic analysis, MRI analysis, data collection and analysis, and writing of manuscript. PN: recruitment of patients, MRI analysis, data collection and manuscript revisions. JS: MRI analysis and manuscript revision. BL: radiographic analysis and manuscript revision. LD: Study design and manuscript revision. CT: Study initiation and design, recruitment of patients, critical revision of the manuscript.

Conflict of interest

All authors state no conflicting interest. None of the funding sources had any involvement in study design, collection, analysis and interpretation of data; in writing of the manuscript; or in the decision to submit the manuscript for publication.

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