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Delayed gadolinium enhanced MRI of cartilage (dGEMRIC) can be effectively applied for longitudinal cohort evaluation of articular cartilage regeneration

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SUMMARY

Objective: Delayed gadolinium enhanced magnetic resonance imaging (MRI) of cartilage (dGEMRIC) facilitates non-invasive evaluation of the glycosaminoglycan content in articular cartilage. The primary aim of this study was to show that the dGEMRIC technique is able to monitor cartilage repair following regenerative cartilage treatment.
Design: Thirty-one patients with a focal cartilage lesion underwent a dGEMRIC scan prior to cartilage repair surgery and at 3 and 12 months follow-up. At similar time points clinical improvement was monitored using the Knee injury and Osteoarthritis Outcome Score (KOOS) and Lysholm questionnaires. Per MRI scan several regions-of-interest (ROIs) were defined for different locations in the joint. The dGEMRIC index (T1gd) was calculated for each ROI. Repeated-measures analysis of variance (RMANOVA) analysis was used to evaluate improvement in clinical scores and MRI T1gd over time. Also regression analysis was performed to show the influence of local repair on cartilage quality at distant locations in the knee.
Results: Clinical scores and the dGEMRIC T1gd per ROI showed a statistically significant improvement ($P < 0.01$), from baseline, at 12 months follow-up. Also, improvement from baseline in T1gd of the ROI defining the treated cartilage defect showed a direct relationship ($P < 0.007$) to the improvement of the T1gd of ROI at other locations in the joint.
Conclusions: The dGEMRIC MRI protocol is a useful method to evaluate cartilage repair. In addition, local cartilage repair influenced the cartilage quality at other location in the joint. These findings validate the use of dGEMRIC for non-invasive evaluation of the effects of cartilage regeneration.

Introduction

Focal articular cartilage lesions in the knee are frequently treated by microfracture or autologous chondrocyte implantation (ACI)[1]. Treatment failure, is often related to inadequate tissue regeneration[2]. Also, good structural repair at short-term follow-up showed to result in good clinical outcome at later time points[3,4].

In clinical trials, the success of cartilage regeneration is usually determined by histological evaluation of regenerated tissue obtained from an additional cartilage biopsy from the newly formed tissue. The disadvantages of a cartilage biopsy and the main reasons for which it has not been introduced as a standard protocol in clinical practice, are the invasive nature of the procedure and the fact that it only provides local information. Therefore, a non-invasive method to determine tissue organization and to assess the distribution of relevant articular cartilage matrix proteins would be of great value in the evaluation of tissue regeneration.

The non-invasive MR imaging technique called delayed gadolinium enhanced magnetic resonance imaging (MRI) of cartilage (dGEMRIC) can be used to assess the concentration of glycosaminoglycans (GAGs) in the extracellular cartilage matrix[5]. This technique is based upon the negatively charged ions of the T1-shortening contrast agent gadolinium diethylene triamine pentaacetic acid ($Gd\text{-}DTPA^{2-}$, Magnevist) that distribute inversely proportional to the

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concentration of the also negatively charged GAGs in articular cartilage. The Gd-DTPA^{2-} concentration per voxel is described by means of the dGEMRIC index (T1gd) which is calculated from the five different inversion times using a curve fitting method. In areas with low GAG the calculated T1gd will be low, and *vice versa*. A good correlation was found between the biochemically determined GAG contents and the related T1gd times in *ex vivo* studies[5,6]. In addition, it was shown that the dGEMRIC technique can be used to evaluate the quality of articular cartilage after osteochondral autologous transplantation, high tibial osteotomy and matrix-assisted ACI (MACI)[7–11].

In addition to the availability of techniques evaluating the outcome of defect treatment, it is becoming increasingly evident that its success is directly dependent on patient characteristics[12]. Factors such as age and gender of the patient and size, age and location of the focal lesion were shown to influence clinical outcome after regenerative cartilage therapy[12]. However, it is not known to what extent these characteristics also affect the biological repair response.

Therefore, the primary aim of this study was to show that the dGEMRIC technique is able to monitor cartilage repair following regenerative cartilage treatment. We also evaluated to what extent local cartilage repair influences the cartilage quality in the whole knee. Also, specific patient and defect characteristics were evaluated for their influence on cartilage repair.

Material and methods

General study outline and patient population

This study was conducted with approval of the institutional ethical committee under protocol number 08-022/E. Patients with a substantial decrease in sports participation or limitations in activities of daily living combined with a strong suspicion of a focal (osteo)chondral lesion on MRI were planned for arthroscopy and indicated for treatment, with either microfracture, MACI, ChondroCelect or Chondron treatment[13]. These patients were eligible for inclusion in this study. If patients signed consent a preoperative dGEMRIC scan was obtained. Patients with general contraindications for MRI scanning, a known allergic reaction to gadolinium-containing contrast agents or with a history of kidney pathology were considered not eligible for inclusion. If, during arthroscopy, the treating physician found that the lesion or other cartilage surfaces were not suitable to receive any of the abovementioned treatments, the included patient was excluded from the study. From April 2009 to March 2010 a total of 40 patients diagnosed with a symptomatic (osteo)chondral focal articular cartilage lesion met the inclusion criteria and were willing to participate in this study. The study procedures and risks were explained and, after a minimum of 14 days, informed consent was obtained by a physician not involved in the diagnostic and therapeutic process (JEJB). One patient was excluded when receiving her first study MRI because of MRI artefacts possibly resulting from previous anterior cruciate ligament reconstruction. In addition, seven patients were excluded during surgery for two reasons; they either showed generalized cartilage degeneration ($n = 2$) or the characteristics of the lesion were not suitable for abovementioned treatments ($n = 5$). One patient was lost to follow-up at 12 months. The baseline characteristics of the 31 patients who were included and completed the study are provided in Table I. All included patients were evaluated before surgery (on average 33 ± 18 days, range 1–78 days) as well as 3 and 12 months after surgery by a dGEMRIC examination and clinical questionnaires.

Table I
Baseline characteristics

	Patients ($n = 31$)
Gender	
Male *n* (%)	23 (74%)
Female *n* (%)	8 (26%)
Age mean ± SD	36 ± 11
<30 jr *n* (%)	12 (39%)
>30 jr *n* (%)	19 (61%)
Type of treatment	
MACI/characterized chondrocyte implantation (CCI) *n* (%)	12 (39%)
Microfracture (MF) *n* (%)	12 (39%)
Chondron *n* (%)	7 (22%)
Defect age* mean (months) ± SD	24 ± 17
<2 y *n* (%)	12 (50%)
>2 y *n* (%)	12 (50%)
Defect size mean (cm^2) ± SD	4 ± 2
<3 cm^2	12 (39%)
>3 cm^2	19 (61%)

* Defect age from Chondron treatment patients is missing.

Cartilage evaluation by dGEMRIC

All dGEMRIC scans were performed on a 1.5-T clinical MRI scanner (Achieva, Philips Healthcare, Best, The Netherlands) using a dedicated eight-element sense knee coil as a receiver (Philips Healthcare, Best, The Netherlands). Scanning took place 90 min after intravenous injection of Magnevist (Gd-DTPA^{2-}, Bayer, Germany) at a dose of 0.2 mmol/kg body weight. After survey scans, a transient field echo (TFE) pulse sequence was used for dGEMRIC with five different inversion delay times (50, 150, 350, 650 and 1650 ms), as previously described by McKenzie *et al.*[14] A total of 36 partitions were obtained with a 256 × 232 in plane acquisition matrix resulting in a voxel size of 0.625 × 0.625 × 3 mm^3, using an echo time of 4.3 ms, a repetition time of 10 ms and a flip angle of 20 degrees. The average T1Gd per region-of-interest (ROI) was calculated after voxelwise fitting of the dGEMRIC signal equation as a function of inversion time using the Levenberg–Marquardt nonlinear least-squares method implemented in in-house developed software. On the sagittal images obtained in the dGEMRIC scan with an inversion delay time of 350 ms a total of six different ROIs (Fig. 1) were drawn using a smartboard with projection on an interactive screen. The *defect* ROI was the region of the treated defect. The cartilage segmentation in the defect ROI was separated from the adjacent (non) defect cartilage using the length, width and size of the defect (obtained from surgery reports). Based on the voxel size of the obtained dGEMRIC scans we calculated the number of slices and width of the defect on the sagittal images for segmentation. In the articular cartilage directly opposing and articulating with the treated defect the *articulating* ROI was drawn. The three joint compartments, patellofemoral, lateral and medial tibiofemoral, were, depending on the site of the cartilage defect, separately identified as the *treated* ROI and two *other* ROIs. Finally a *whole knee* ROI was created that consisted of a segmentation of all the articular surfaces in the knee. All segmentations were performed by one person (JEJB) and consensus with an experienced knee specialized orthopedic surgeon was obtained in case of any doubts. Baseline ROIs were used and plotted on the follow-up scans at 3 and 12 months to guarantee similar sized ROIs over time. For a set of 15 scans all ROIs were, with an interval of 1 month, repeated by the same observer to evaluate the internal consistency and reliability of the segmentation process.

Evaluation of clinical outcome

The clinical treatment outcome was assessed using two different questionnaires both validated for the evaluation of the clinical status of patients treated for an articular cartilage lesion[15,16].

The Knee injury and Osteoarthritis Outcome Score (KOOS) was designed to evaluate the short- and long-term follow-up of

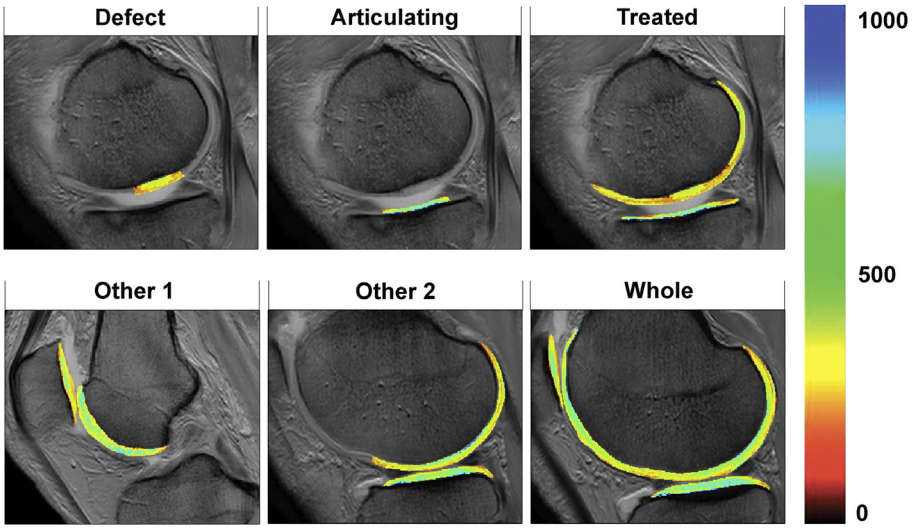

Fig. 1. ROIs. Sagittal MRI slices of the scan with 350 ms inversion delay time showing example ROI segmentations as a color overlay. The color bar represents the calculated T1gd in milliseconds, where a high T1gd (1000 ms) is depicted as blue and a low T1gd (nearly 0 ms) as red.

treatment of knee injury and knee osteoarthritis. Recently this questionnaire was validated to measure the clinical condition in patients after regenerative cartilage surgery[15]. The KOOS consists of five subdomains; symptoms, pain, activities of daily living, function in sport and recreation and knee-related quality of life. The KOOS score per subdomain (score 0–100) was calculated using the free available scoring sheet on the KOOS website (http://www.koos.nu/).

The Lysholm questionnaire was initially designed to evaluate the functional disabilities resulting from ligamentous injury. Recently, this questionnaire has also been validated to asses articular cartilage damage[16]. The questionnaire consists of eight domains (pain, instability, locking, swelling, limping, walking stairs, squatting and keeping support) and translates to a score between 0 and 100 (normal knee function).

Statistical analysis

All statistical analyses were performed using SPSS statistical software version 15.0 (Chicago, USA). Internal consistency of the segmentation process was performed by the Cronbach's alpha and the reliability using the intraclass correlation coefficient (ICC).

Repeated-measures analysis of variance (ANOVA)

Absolute improvement from baseline at 3 and 12 months follow-up for (subdomains of) the clinical questionnaires and ROIs was calculated (by extracting the baseline values from the 3 and 12 month values) and tested using a repeated-measures ANOVA with a repeated model fit. All variables showed a normal distribution (Kolmogorov–Smirnov $P > 0.05$) equality of variance (Levene's test $P > 0.05$) and met the assumption of sphericity (Mauchly's test $P > 0.32$) and could therefore validly be included in the repeated-measures model.

To correct for a false positive interpretation of statistical significance among the multiple tests that were performed to show the, possible, improvement over time of one variable a Bonferroni correction was performed following the repeated-measures model. Improvement over time is, for all variables, presented as average ± standard deviation.

Conditions for regression analysis

A regression analysis was performed to evaluate possible relations between our outcome variables. Before valid inclusion into the regression model, all variables were subjected to a normality test by the Kolmogorov–Smirnov coefficient, a test for intervariable correlation and multicollinearity (Pearson correlation coefficient and the variance inflation factor) and an assessment for autocorrelation (correlation within a single variable) with the Durbin–Watson coefficient. Also, in multiple regression analysis, the unstandardized residuals were evaluated for the absence of intercorrelation and scatterplots were created to test normal residual distribution and homoscedasticity. A Kolmogorov–Smirnov coefficient with $P > 0.05$ indicates normal distribution while a variance inflation factor close to 0 or >5 was considered indicative of multicollinearity. A Durbin–Watson coefficient close to 0 is related to strong negative autocorrelation, whereas a Durbin–Watson close to 4 suggests strong positive autocorrelation.

For each regression analysis, the *B*-coefficient, standard error of the *B*-coefficient, the 95% confidence interval (95% CI), the R^2 and *P*-value of the model were obtained. The *B*-coefficient explains the relation between the predictor and dependent variable where an increase of 1 unit of the predictor results in an increase of the dependent variable by the value of *B*. This relation is statistically significant if the $P < 0.05$ and causality counts for the percentage expressed by the R^2.

Linear regression analysis

Linear regression analysis was performed to evaluate whether local regeneration (expressed by the 12 months improvement in measured T1gd from baseline in the defect ROI) influences other joint compartments. For this, a single linear regression model was applied with the absolute improvement of measured T1gd in the defect ROI as a predictor variable and the absolute improvement of measured T1gd of the other ROIs (articulating, treated, other 1, other 2 and whole) as dependent variables.

Multiple regression analysis

Multiple linear regression with backward elimination was performed to test what patient characteristics were related to improvement in defect T1gd after 12 months. For all statistical analysis a *P*-value of $P < 0.05$ was considered statistically significant.

Results

dGEMRIC and clinical scores; improvement from baseline

The segmentation process was valid with a Cronbach's alpha of 0.86 and an ICC of 0.91.

At baseline, the T1gd ranged from 365 to 484 ms for the different ROIs (defect 365 ± 46, articulating 484 ± 125, treated 421 ± 48, other 1 422 ± 60, other 2 448 ± 68, whole 432 ± 54). The KOOS scores at baseline were lowest for the sports and quality of life subdomains (pain 59 ± 19, activity of daily living 65 ± 20, symptoms 62 ± 18, sports 27 ± 22, quality of life 24 ± 15). The baseline Lysholm score was 48 ± 21 points.

Except for the articulating ROI, the T1gd indices at 3 months after surgery were slightly, but statistically non-significantly, decreased compared to the baseline values (Table II, defect 362 ± 54, articulating 481 ± 171, treated 407 ± 68, other 1 411 ± 61, other 2 419 ± 55, whole 415 ± 58). After 12 months follow-up, the T1gd of the defect and the articulating ROI showed the largest, statistically significant ($P < 0.01$) improvement from baseline (defect 468 ± 91, articulating 622 ± 241), which was also clearly visible on the dGEMRIC images (Fig. 2). In addition, the T1gd of the other ROIs (treated 481 ± 91, other 1 503 ± 85, other 2 680 ± 63, whole 484 ± 67) also showed a clear, and statistically significant ($P < 0.01$), improvement from baseline.

At 3 months after surgery, the clinical scores did not show a statistically significant change from baseline (Table II). However, at 12 months follow-up all but three patients showed clearly improved clinical scores. Improvement from baseline was noted on the Lysholm, the KOOS subdomains and the KOOS overall scores ($P < 0.01$) (Table II).

Regression analysis; effect of defect treatment on distant cartilage quality

All variables in the regression analysis had a normal distribution (normality tests $P > 0.358$) and no multicollinearity or autocorrelation was found (variance inflation factor, 1.000; Durbin–Watson range, 2.199–2.510). Also scatterplots of model residuals showed normal residual distribution and homoscedasticity of residuals.

The increase in T1gd after 12 months at the *defect* ROI was significantly related to the T1gd increase of the other ROIs in the joint (Table III). The *B*-values ranged from 0.787 to 0.567 indicating that for each millisecond increase in T1gd at the treated defect after 12 months, the T1gd of the cartilage at another location in the joint increased with 0.787–0.567 ms.

Multiple regression analysis showed that the patient characteristics (gender, patient age, defect age and defect size) did not influence ($P > 0.070$) the improvement in T1gd after 12 months for the *defect* ROI. However, defect size and patient age were shown to influence the improvement in T1gd of the *whole* ROI at 12 months after surgery. A defect size >3 cm^2 was related to 58 ± 24 less increase ($P = 0.024$) in T1gd of the joint as a whole after 12 months compared to defects <3 cm^2 and in patients <30 years old a 152 ± 47 stronger increase ($P = 0.005$) in the T1gd was found compared to those >30 years old at 12 months after surgery.

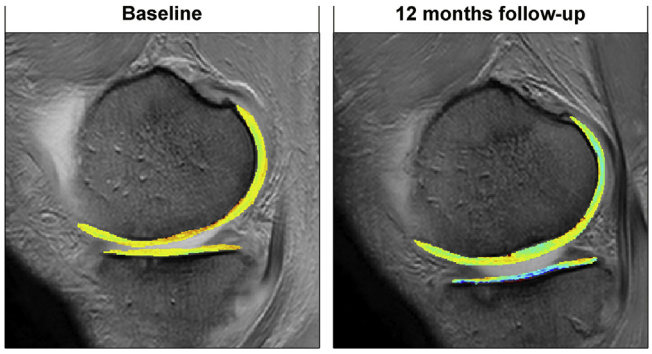

Fig. 2. dGEMRIC at baseline and 12 months follow-up. The blue pixels represent a high T1gd (1000 ms) while a low T1gd of 0 is labeled as red. At the preoperative situation a clear change in signal (from yellow to red) is visible at the site of the lesion when compared to the rest of the knee. At 12 months after surgery the overall signal in the knee is improved (more blue–green) with a clear signal improvement at the treated defect site.

Discussion

This study evaluated the feasibility of non-invasive monitoring by dGEMRIC of defect repair and general tissue integrity of cartilage in the joint after cartilage repair surgery. The dGEMRIC scanning technique was useful in detecting local cartilage repair in a focal defect 1 year after treatment, which was accompanied by clearly improved clinical scores. In addition, local improvement of T1gd was directly related to the improvement of cartilage quality in other joint compartments. Also, patient age and defect size influenced the treatment response of the articular cartilage in the whole knee.

The International Cartilage Research Society has recently published several guidelines for histological and MRI based evaluation of cartilage repair studies[17,18]. Histological evaluation of newly formed cartilage provides information on the structural

Table II
Clinical outcome evaluation

	Baseline − 3 months	Baseline − 12 months
KOOS questionnaire		
Pain	12 ± 4 (5–20)*	21 ± 4 (13–29)*
Symptoms	4 ± 4 (−4–12)	15 ± 4 (7–23)*
Activity	6 ± 4 (−1–14)	20 ± 4 (13–27)*
Sports	−1 ± 4 (−10–7)	29 ± 5 (19–38)*
QoL	5 ± 3 (−1–11)	20 ± 4 (13–28)*
Overall KOOS	6 ± 3 (0–13)	20 ± 3 (14–27)*
Lysholm	9 ± 4 (1–17)	28 ± 3 (21–35)*
ROIs		
Defect	−4 ± 11 (−26–18)	103 ± 13 (76–130)*
Articulating	20 ± 28 (−36–76)	158 ± 46 (65–252)*
Treated	−19 ± 10 (−39–2)	49 ± 18 (12–86)*
Other 1	−11 ± 10 (−30–9)	78 ± 16 (44–111)*
Other 2	−16 ± 10 (−38–5)	44 ± 14 (15–72)*
Whole	−10 ± 11 (−32–12)	51 ± 15 (13–74)*

Improvement from baseline [mean ± SD and (95%CI)] after 3 and 12 months (calculated by extracting the baseline values from the 3 and 12 month values) for both the clinical questionnaires and dGEMRIC ROIs. *$P < 0.01$.

Table III
Defect treatment relates to overall cartilage improvement

Dependent variable	*B*	*P*-value	95%CI lower	95%CI upper
Treated T0T12	0.787	0.001	0.364	1.210
Other 1 T0T12	0.651	0.002	0.253	1.049
Other 2 T0T12	0.567	0.002	0.233	0.901
Whole	0.689	0.001	0.354	1.023

Linear regression analysis using the increase in T1gd from baseline to 12 months at the defect ROI as a predictor for the increase in T1gd from baseline to 12 months at other joint locations/ROIs. The *B*-value represents the increase in the dependent variable when the increase in the predictor is 1. For example, when the T1gd at the defect ROI improves with 1 ms in 12 months' time the T1gd of the treated joint compartment (treated ROI) improves with 0.787 explaining an influence of local regeneration on cartilage quality in locations in the joint.

organization and can help to understand the biological success of tissue regeneration[17]. Disadvantages of histological evaluation are the time consuming processing and the small volume of tissue that can be analyzed. Moreover, the invasive nature of the necessary biopsy makes longitudinal follow-up less desirable from an ethical point of view. Contrast-enhanced MRI scanning protocols, such as dGEMRIC, are able to represent tissue structure and can be readily applied in a longitudinal follow-up. Moreover, with MRI the whole joint can be assessed instead of only small tissue volumes after biopsy.

Overall the dGEMRIC technique is reliable as repeated measurements show a good reproducibility[19–21]. Also the coefficient of variation in the bulk T1gd for certain cartilage ROIs was 5%, ranging from 4.2% to 5.5% for femur and tibia cartilage respectively[19]. However, recent reports question the robustness of the physical properties at which the dGEMRIC technique is based on. The measurement of bulk T1gd values from articular cartilage 1.5 h after scanning is based on the assumption of a steady state concentration gradient at that time[14]. However, recently it was shown that the depth-wise concentration gradient of Gd-DTPA^{2-} is continuously changing which could make bulk ROI measurements less reliable[22]. In addition, the diffusion time of Gd-DTPA^{2-} seemed slower than previously assumed and the distribution of Gd-DTPA^{2-} is also influenced by the collagen content of the articular cartilage[23]. These observations should be taken into account when dGEMRIC data is being evaluated and one should be cautious to directly relate measured T1gd to tissue GAGs. Abovementioned issues are the limitation of dGEMRIC technique and manuscripts that directly relate dGEMRIC findings to tissue GAG. In addition this study could have been strengthened when also other quantitative MRI techniques, such as T2 mapping or proton density sequences, were added to the analysis. In addition, such scanning sequences are more reliable in the assessment of a focal lesion and therefore will lead to a more precise segmentation of the cartilage in the focal defect area. This could prevent from an erroneous baseline T1gd values of the defect ROI resulting from a segmentation that includes limited amounts of the −gadolinium containing− synovial fluid in the defect. Also longer follow-up would have provided more information on the use of non-invasive evaluation tools, such as dGEMRIC, for the evaluation of articular cartilage following cartilage repair.

To our knowledge one study also compared the T1gd values measured in a focal cartilage lesion to those 1 year after matrix-associated ACI[9]. However, the main outcome parameter of that study was to evaluate the zonal distribution of GAGs, using dGEMRIC, in normal and repair tissue. Therefore, the study may have been underpowered ($n = 15$) to show statistically significant T1gd improvement between the preoperative and postoperative scans. Therefore, this is the first study to show that a dGEMRIC scanning protocol can be used to longitudinally show improvement in T1gd, as a possible representation of tissue GAG concentration, following cartilage repair.

Several other groups already used dGEMRIC to evaluate articular cartilage after ACI, but focussed on differences between repair and native tissue, the zonal organization of the newly formed tissue or only performed post-surgery dGEMRIC without baseline measurements[7,9,11,24]. Considering the large variation in T1gd times between patients, it is difficult to define a consensus T1gd that represents acceptable or good quality cartilage after regeneration. Therefore, patient specific baseline measurements are essential when cartilage quality following regenerative surgery is a relevant outcome in a longitudinal study.

During the different phases of cartilage regeneration the organization of matrix constituents and water content change continuously[18]. These factors influence the T1 relaxation time of the newly formed tissue and most likely lead to differences of the measured T1 relaxation times in repair tissue compared to the reference healthy or degenerated cartilage[18]. This should be taken into account when cartilage is being evaluated with the dGEMRIC technique. A direct comparison, using only post-contrast imaging, between repair tissue and other locations in the joint could, therefore, introduce erroneous interpretation of the data and does not represent the true GAG content in articular cartilage[18]. The delta relaxation rate [$\Delta R1 = 1/T1$ precontrast $- 1/T1$(Gd)] corrects for the differences in precontrast T1 and is preferred when different locations in the joint are being evaluated and compared in a cross-sectional study design[18]. However, per location in the joint (either repair or healthy reference tissue) the correlation between the T1gd and $\Delta R1$ is high and separate interpretation of both outcome variables leads to similar conclusions[25]. The absence of precontrast imaging, in this study, combined with a longitudinal evaluation at predefined locations does, for abovementioned reason, not influence data interpretation nor change the final conclusions. In addition, patient comfort will decrease when also a precontrast MRI scan was performed as scanning time would be twice as long.

The clinical benefit following ACI and microfracturing is influenced by specific characteristics of the defect or patient[4,12,26–28]. Also, in specific cases one technique may perform better than the other one does[4,12,27,29]. In this study, the size of the defect and age of the patient showed a direct relation to the overall improvement in T1gd of the articular cartilage in the knee, at 12 months after surgery. This implies that specific biological characteristics of the defect and patient could play a role in the intrinsic repair capacity of the articular cartilage following surgery. The articular cartilage in the knee showed less improvement following cartilage surgery when a large defect (>3 cm^2) had been present. Whether the size of the defect is positively correlated to the severity of disturbance in joint homeostasis remains to be seen, however, the presence of an articular cartilage defect has been shown to induce joint cartilage degeneration[30]. It has also been shown that larger defects, if left untreated, are related to an increased cartilage volume loss[31]. Age influenced the improvement in T1gd following cartilage surgery in this study. Younger patients could be more sensitive for a regenerative response due to the senescence of cells and tissues related to the effects of aging[32].

Based on macroscopic and biochemical evaluation, the treatment of an articular cartilage defect has been related to a decrease in degenerative characteristics at other joint locations[30]. In this study we showed, using regression analysis, that defect treatment is related to the improvement of the T1gd at other locations in the joint which could imply improved cartilage quality. These findings underline the importance of the concept of joint homeostasis and the role for early detection and intervention. The presence of an articular defect should be regarded as indicative of a joint disease rather than a local problem. Timely treatment has been shown to improve clinical outcome, i.e., timely restoration of the joint homeostasis improves the regenerative response of the whole joint[4,12]. Using dGEMRIC, such changes can be monitored thereby providing a reliable imaging tool for the evaluation of cartilage quality in the whole joint following cartilage repair.

In conclusion, this study demonstrates that the dGEMRIC technique can be used to longitudinally measure changes in T1gd following cartilage repair surgery. Also, using dGEMRIC we showed that patient age and defect size influence the improvement in T1gd following cartilage surgery and that local repair influences the T1gd at distant locations in the joint. Taken together, these findings illustrate the value of dGEMRIC for the evaluation of the effects of cartilage repair and clearly indicate a role for early detection and intervention.

Author contributions

Conception and design: JEJ Bekkers, LW Bartels, RJ Benink, AI Tsuchida, KL Vincken, WJA Dhert, LB Creemers, DBF Saris.

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Obtaining of funding: WJA Dhert, LB Creemers, DBF Saris.

Administrative, technical, or logistic support: JEJ Bekkers, AI Tsuchida.

Collection and assembly of data: JEJ Bekkers, LW Bartels, AI Tsuchida, KL Vincken.

Conflict of interest

None of the authors have any conflict of interest related to the work presented in this manuscript.

Role of the funding source

The study sponsors were not involved in/did not have any influence on study design, collection, analysis and interpretation of data, writing of the manuscript; and in the decision to submit the manuscript for publication.

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