

EXTENDED REPORT

Association of changes in delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) with changes in cartilage thickness in the medial tibiofemoral compartment of the knee: a 2 year follow-up study using 3.0 T MRI

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Received 7 December 2012

Revised 14 May 2013

Accepted 29 June 2013

Published Online First

19 July 2013

ABSTRACT

Objective To determine the association between changes in the delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) index over 2 years as a measure of cartilage proteoglycan concentration, with changes in cartilage thickness in the medial tibiofemoral compartment of knees in middle-aged women.

Methods One hundred and forty-eight women (one knee for each subject) aged ≥ 40 years were included. 3.0 T MR images of the knee were acquired at baseline, 1 year and 2 years. Three-dimensional (3D) spoiled gradient recalled echo (SPGR) sequences (for cartilage thickness) and 3D inversion recovery-prepared SPGR sequences after dGEMRIC were acquired. Segmentation was performed in the medial central (weight-bearing) femur and tibia to determine cartilage proteoglycan concentration and thickness. The association of change in the dGEMRIC indices between baseline and 1-year follow-up with (a) concomitant changes in cartilage thickness and (b) change in cartilage thickness between 1 and 2 years was assessed using linear regression.

Results In the whole-sample model, a decrease in dGEMRIC indices over time at the central medial femur significantly predicted an increase in cartilage thickness at both the central medial femur ($p=0.008$) and the medial tibia ($p=0.04$).

Conclusions A decrease in dGEMRIC indices was associated with an increase in cartilage thickness in the medial compartment. Our results suggest that an increase in cartilage thickness may also be related to a decrease in proteoglycan concentration, which may represent swelling of cartilage in early stages of degeneration.

INTRODUCTION

Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) can assess the composition of the cartilage matrix before morphological surface changes appear.^{1–3} It was specifically created to assess the glycosaminoglycan (GAG) concentration of the cartilage matrix.^{4–5} Ions within the interstitial fluid of cartilage are distributed in relation to the concentration of negatively charged GAG molecules (proteoglycan

content). Gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA^{2–}), the contrast agent used in dGEMRIC, distributes in areas within the cartilage where the negatively charged GAG content is low. Since the concentration of Gd-DTPA^{2–} can be approximated by measuring T1, T1 assessment of cartilage after intravenous administration of Gd-DTPA^{2–} allows evaluation of the GAG concentration of cartilage.⁶ The dGEMRIC measurements have been validated in clinical studies, corresponding to reference standard measurements for GAG histology and biochemistry.⁵ dGEMRIC has been shown to demonstrate variations in morphologically intact cartilage and may have a bearing on the development of knee osteoarthritis (OA).⁷ Previous experimental studies demonstrated the usefulness of dGEMRIC measurements in the detection of alterations in the GAG content of cartilage matrix, when using histological data as the reference.^{8–9}

Compositional MRI techniques have the potential to become markers of the incidence and progression of OA, especially in the earliest stages of disease and could be useful in clinical trials when testing disease-modifying OA drugs.^{10–11} Before dGEMRIC can be validated as a marker, an association must be shown between worsening of the dGEMRIC index and morphological changes over time. One previous study showed that a low dGEMRIC index at baseline was not associated with longitudinal cartilage thinning, after correction for multiple testing.¹²

MRI accurately measures cartilage loss longitudinally via quantitative assessment.^{13–16} Algorithms have been developed for measuring cartilage thickness in defined subregions of the femorotibial joint,^{17–18} and subregional changes in the central and external medial tibia and in the central part of the weight-bearing femoral condyle have been shown to exceed changes in other subregions of the medial femorotibial compartment.^{19–20}

The aim of this study was to assess the association of changes in dGEMRIC indices with changes in cartilage thickness in the medial tibiofemoral compartment of knees in a sample of middle-aged women, over a 2-year period, using 3.0 T MRI.



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To cite: Crema MD, Hunter DJ, Burstein D, et al. *Ann Rheum Dis* 2014;**73**:1935–1941.

MATERIAL AND METHODS

Subjects

A total of 180 women aged ≥ 40 years participated in the study. The recruitment has been described in detail previously.^{12 13 20} Briefly, subjects were recruited at seven clinical centres to participate in a longitudinal 2-year observational study to evaluate progression of knee OA. Conventional weight-bearing anteroposterior knee radiographs were obtained at each centre to establish the baseline status of knee OA using the Kellgren and Lawrence (KL) grading scale.²¹

Inclusion criteria for OA participants were frequent symptoms, mild to moderate radiographic OA in the medial compartment (KL 2 or 3), a body mass index (BMI) of ≥ 30 and a medial tibiofemoral joint space width ≥ 2 mm in a posteroanterior modified Lyon–Schuss radiographic view.²² Inclusion criteria for the control group were complete absence of bilateral knee symptoms, KL grade ≤ 1 in either knee and a BMI ≤ 28 . Furthermore, knee alignment was determined by the anatomic-axis angle measured on the baseline posteroanterior Lyon–Schuss radiographs, using the method described by Kraus *et al.*²³ The study was conducted in compliance with local institutional review boards, informed consent regulations, the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki.

All subjects with missing data on cartilage thickness in the medial tibiofemoral compartment, on medial tibiofemoral dGEMRIC, on demographic and KL grade data or on knee alignment data were excluded from the analysis (figure 1).

MR imaging protocol

Siemens Magnetom Trio 3.0 Tesla (T) magnets (Siemens AG, Erlangen, Germany) were used at three of the seven study sites, two sites used Signa Excite/Genesis 3.0 T MRI long-bore magnets and two used General Electric short-bore magnets (GE Healthcare Technologies, Waukesha, Wisconsin, USA).

For assessment of cartilage thickness, double oblique coronal spoiled gradient recalled acquisition at steady state (SPGR) sequences with selective water excitation were acquired at baseline, 1 year and 2 years with an in-plane resolution of $0.31 \text{ mm} \times 0.31 \text{ mm}$ and a slice thickness of 1.0 mm (TE=7.2–8.5 ms, TR=16–17 ms, flip angle=12°, bandwidth=31.25 kHz (GE) or 130 Hz/pixel (Siemens), matrix size=512×512).

For dGEMRIC assessment, subjects were intravenously injected with 0.2 mmol/kg of Gd-DTPA²⁻ and asked to walk or

use a pedal exerciser for 10 min to aid the transport of the contrast agent into cartilage. Sagittal 3D inversion recovery-prepared SPGR sequences with selective water excitation were obtained 90 min after Gd-DTPA²⁻ administration, for baseline and 1-year imaging, with similar parameters as described above.

A sagittal fat-suppressed 2D dual-echo fast spin echo sequence was also acquired at baseline and at 1 year with an in-plane resolution of $0.63 \text{ mm} \times 0.63 \text{ mm}$ and a slice thickness of 3.0 mm (TE=9/39 ms, TR=2700–3600, flip angle=170°, bandwidth=32 kHz (GE) or 199 Hz/pixel, (Siemens), matrix size=256×256).

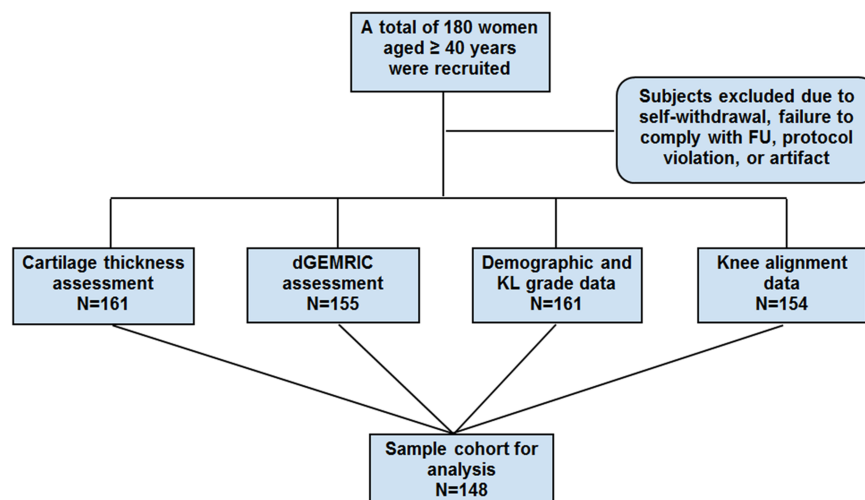
Cartilage thickness measurement

Seven technicians with formal training and thorough experience in cartilage segmentation performed the segmentation of the medial femorotibial cartilage on all the coronal images.^{12 13 20} Images were read in pairs, with blinding to the time point of acquisition. Manual tracing of the total subchondral bone area and the cartilaginous joint surface area of the medial tibia and the central (weight-bearing) medial femoral condyle was performed. Femoral cartilage was analysed in a region of interest between the intercondylar notch and 60% of the distance to the posterior end of the femoral condyles in the coronal view.²⁰ All segmented slices of each dataset were reviewed by a single person (FE) who performed quality control of all segmentations.^{24 25} Morphological cartilage changes were computed using the difference of the mean cartilage thickness over the total area of subchondral bone between baseline and 1 year, as well as between the 1-year and 2-year follow-up, at either the medial tibia or central medial femoral condyle. Test–retest measurements of the mean cartilage thickness over the total area of subchondral bone using total plates to ensure reproducibility have been previously described in detail.¹³

dGEMRIC assessment

dGEMRIC was assessed at baseline and at 1 year. For each dataset, one medial tibiofemoral sagittal section that included both articular cartilage and medial meniscus was chosen for analysis (matched for baseline and follow-up images). This section was located in the middle of the medial tibiofemoral compartment using coronal images as a guide. Areas of articular cartilage were hand-segmented using sagittal dual-echo T2-weighted images as a guide. T1(Gd) maps were then generated using custom-coded software (MRI Mapper; Beth Israel Deaconess

Figure 1 Flow chart of the study cohort. Data were missing owing to self-withdrawal, failure to comply with follow-up, protocol violation or artefacts during MRI acquisition. In total, 32 subjects were excluded. FU, follow-up; KL, Kellgren and Lawrence.



Medical Center) in MatLab 7 that uses a pixel-by-pixel three-parameter T1 fit.²⁶ The reported T1(Gd) value (dGEMRIC index) is the average of the T1(Gd) values in a given region of interest. Areas of cartilage with a lower dGEMRIC index are assumed to have low concentration of GAG.²⁷

Three regions were segmented in the articular cartilage of each section: the first contained the central medial femoral cartilage, which was defined as cartilage between the outer edges of the anterior and posterior horns of the meniscus; the second contained all of the medial tibial plateau cartilage; and the third contained the posterior medial femoral cartilage, posteriorly to the outer edge of the posterior horn of the meniscus. The posterior region was not considered in our analysis since it was not segmented for cartilage thickness assessment.

We considered different groups according to changes in the dGEMRIC indices over time in the same medial region (figure 2): (a) the increased group (dGEMRIC index higher at 1 year than at baseline); (b) the decreased group (dGEMRIC index lower at 1 year than at baseline); and (c) the stable group (dGEMRIC index stable at 1 year compared with baseline). Regions with stable dGEMRIC indices were not considered in the analysis.

Statistical analyses

First, we assessed the association of changes in the dGEMRIC indices with changes in cartilage thickness in groups of knees defined by KL grade: (a) KL grades 0 and 1; (b) KL grade 2; (c) KL grade 3. Owing to this stratification, we had insufficient

power to test the effects of the increased and decreased dGEMRIC groups separately. For each region, we determined the associations of changes in dGEMRIC indices at 1 year with changes in cartilage thickness at 1 year. We also determined the association between changes in dGEMRIC indices at 1 year with changes in cartilage thickness during the second year. Associations were obtained using linear regression models, with adjustments for age, BMI and knee malalignment. The β_1 coefficients from the linear regression models represent the level of change in cartilage thickness over time (Y; outcome) measured for one unit 'decrease' (worsening in GAG concentration) in dGEMRIC values (predictor), as expressed by, $Y = \beta_0 + \beta_1 X$ (where X represents the amount of change in dGEMRIC at 1 year from baseline). A positive β_1 value represents a decrease in both cartilage thickness and dGEMRIC; a negative β_1 value represents an increase in cartilage thickness but a decrease in dGEMRIC.

Second, we used all the knees in the study to assess the same associations as described above in which we considered the increased and decreased dGEMRIC groups separately. We adjusted the results for age, BMI, knee malalignment and for the KL grade. In each group considered in the second analysis, a positive β_1 value represents a change in cartilage thickness in the same direction of change as the dGEMRIC index; a negative β_1 value represents a change in cartilage thickness in the opposite direction to the change in the dGEMRIC index.

We also investigated whether there was any association of changes in the dGEMRIC index at the central medial femur

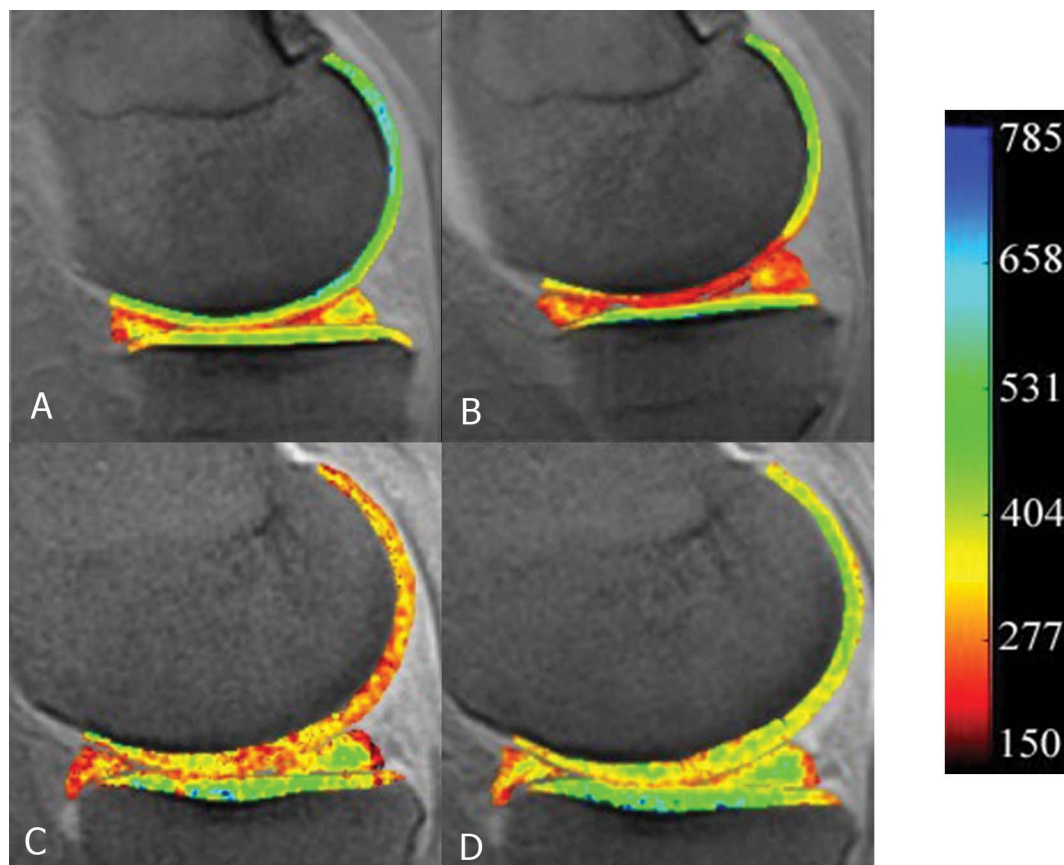


Figure 2 Changes in delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at the central medial femur over 1 year: (A) baseline and (B) the decrease at 1 year in the same medial compartment. Changes in dGEMRIC at the central and posterior medial femur: (C) baseline and (D) the increase at 1 year in the same medial compartment. Corresponding colour map; value in milliseconds.

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with changes in cartilage thickness at the medial tibia and vice versa. All statistical analyses were performed using SAS software (SAS Institute Inc, Cary, North Carolina, USA, release V9.1).

RESULTS

Participants' characteristics and mean dGEMRIC indices

The study sample comprised 148 women (one knee for each subject; 296 medial regions), with a mean age of 56.8 years (± 8.7) and mean BMI of 29.3 kg/m² (± 7.5). Of these, the control group contained 92 (62.2%) subjects, with a mean age of 56.3 (± 9) years and a mean BMI of 24.8 (± 4.4). In the control group, 88 knees had baseline KL grade 0 and four had baseline KL grade 1. The OA group had 56 subjects (37.8%), with a mean age of 57.4 (± 8.2) years and a mean BMI of 36.7 (± 5.4). In the OA group, 30 knees had baseline KL grade 2 and 26 had baseline KL grade 3. The only significant difference between the OA group and the control group was in the mean BMI ($p < 0.05$).

At the central medial femur, the mean of the dGEMRIC indices at baseline was 581.1 ms (SD 122.2 ms; range 263–978 ms) and at 1 year was 599.1 ms (SD 126.2 ms; range 318–905 ms). At the medial tibia, the mean dGEMRIC index at baseline was 563.1 ms (SD 102.3 ms; range 300–818 ms) and at 1 year was 611.6 ms (SD 107.3 ms; range 351–1032 ms).

Association of changes in dGEMRIC indices with changes in cartilage thickness stratified by the KL grade

In knees with baseline KL grades 0 and 1 (table 1), there were no significant associations, after adjustments, between changes in dGEMRIC indices and changes in cartilage thickness when changes in the same region were considered. However, a decrease in dGEMRIC indices at the central medial femur from baseline to 1 year follow-up was significantly associated with an increase in cartilage thickness at the medial tibia from the 1- to 2-year follow-up, after adjustments ($p = 0.02$).

In knees with baseline KL grade 2 (table 1), there was a significant association at the central medial femur between the decrease in dGEMRIC indices and the increase in cartilage thickness in the first year, after adjustments ($p = 0.04$).

In knees with baseline KL grade 3, there were no significant associations between changes in dGEMRIC indices and changes in cartilage thickness (data not shown).

Association of changes in dGEMRIC indices with changes in cartilage thickness in the whole sample stratified by dGEMRIC groups: increase and decrease

Of 296 subregions assessed, in the first year 185 (62.5%) showed an increase in dGEMRIC indices, 107 (36.1%) showed a decrease in dGEMRIC indices and in four (1.4%) the dGEMRIC indices remained the same. We found that a decrease in dGEMRIC indices at the central medial femur in the first year was significantly associated with an increase in cartilage thickness in the second year at both the central medial femur ($p = 0.01$) and at the medial tibia ($p = 0.04$), after adjustments (table 2). No significant associations were found for the increased dGEMRIC group.

DISCUSSION

We demonstrated that a decrease in the dGEMRIC index was associated with an increase in cartilage thickness in certain regions of the medial compartment of the knee. To the best of our knowledge, this is the first study to assess the associations of changes in dGEMRIC indices with changes in cartilage thickness.

Previous studies attempted to show that alterations in cartilage using compositional MRI are associated with morphological changes in cartilage. In a study which used data from the OA Initiative, Joseph *et al*²⁸ evaluated the relationship between baseline T2 values of cartilage and morphological changes of cartilage in the patella over 3 years and showed that knees with increased cartilage lesion scores had significantly greater baseline

Table 1 Associations of changes in dGEMRIC indices with changes in cartilage thickness over time, stratified by the Kellgren and Lawrence (KL) grade

Outcome: changes in cartilage thickness		Predictor: decrease in dGEMRIC from baseline to 1 year	Unadjusted		Adjusted*	
Timeline	Region		β1(SE)	p Value	β1(SE)	p Value
KL grades 0 and 1						
1 Year–baseline	Medial tibia	Medial tibia	−0.000025 (0.000040)	0.54	−0.000020 (0.000045)	0.65
	Medial tibia	Central medial femur	0.000066 (0.000044)	0.14	0.000061 (0.000047)	0.20
2 Years–1 year	Medial tibia	Medial tibia	−0.000062 (0.000057)	0.28	−0.000044 (0.000071)	0.54
	Medial tibia	Central medial femur	−0.000150 (0.000061)	0.02†	−0.000176 (0.000072)	0.02†
1 Year–baseline	Central medial femur	Medial tibia	0.000072 (0.000071)	0.31	0.000097 (0.000078)	0.22
	Central medial femur	Central medial femur	0.000122 (0.000078)	0.12	0.000033 (0.000084)	0.70
2 Years–1 year	Central medial femur	Medial tibia	−0.000082 (0.000079)	0.30	−0.000014 (0.000097)	0.88
	Central medial femur	Central medial femur	−0.000014 (0.000088)	0.87	0.000025 (0.000104)	0.81
KL grade 2						
1 Year–baseline	Medial tibia	Medial tibia	0.000125 (0.000113)	0.28	0.000137 (0.000120)	0.26
	Medial tibia	Central medial femur	0.000010 (0.000103)	0.92	0.000041 (0.000111)	0.71
2 Years–1 year	Medial tibia	Medial tibia	−0.000170 (0.000155)	0.28	−0.000258 (0.000148)	0.09
	Medial tibia	Central medial femur	0.000033 (0.000141)	0.82	0.000125 (0.000139)	0.38
1 Year–baseline	Central medial femur	Medial tibia	0.000067 (0.000164)	0.69	0.000113 (0.000178)	0.53
	Central medial femur	Central medial femur	−0.000387 (0.000164)	0.03†	−0.000378 (0.000176)	0.04†
2 Years–1 year	Central medial femur	Medial tibia	−0.000175 (0.000253)	0.49	−0.000378 (0.000214)	0.09
	Central medial femur	Central medial femur	0.000213 (0.000222)	0.35	0.000344 (0.000192)	0.09

*Adjusted for age, body mass index and knee malalignment.

†Statistical significance defined as $p < 0.05$.

dGEMRIC, delayed gadolinium-enhanced MRI of cartilage.

Table 2 Associations of changes in dGEMRIC indices with changes in cartilage thickness over time, stratified by changes in dGEMRIC: increased and decreased dGEMRIC groups

Outcome: changes in cartilage thickness			Unadjusted		Adjusted*	
Timeline	Region	Predictor: decrease in dGEMRIC from baseline to 1 year	β 1 (SE)	p Value	β 1 (SE)	p Value
Decreased dGEMRIC group†						
1 Year–baseline	Medial tibia	Medial tibia	0.000058 (0.000117)	0.62	0.000180 (0.000158)	0.26
	Medial tibia	Central medial femur	0.000170 (0.000091)	0.07	0.000119 (0.000097)	0.23
2 Years–1 year	Medial tibia	Medial tibia	−0.000164 (0.000172)	0.35	−0.000093 (0.000211)	0.66
	Medial tibia	Central medial femur	−0.000307 (0.000131)	0.02†	−0.000304 (0.000146)	0.04†
1 Year–baseline	Central medial femur	Medial tibia	0.000032 (0.00021)	0.88	0.000186 (0.000212)	0.39
	Central medial femur	Central medial femur	0.000384 (0.000173)	0.03†	0.000287 (0.000167)	0.09
2 Years–1 year	Central medial femur	Medial tibia	−0.000192 (0.000248)	0.44	−0.000141 (0.000304)	0.65
	Central medial femur	Central medial femur	−0.000446 (0.000178)	0.02†	−0.000486 (0.000174)	0.01†
Increased dGEMRIC group‡						
1 Year–baseline	Medial tibia	Medial tibia	0.000019 (0.000073)	0.80	0.000019 (0.000079)	0.81
	Medial tibia	Central medial femur	−0.000039 (0.000088)	0.66	−0.000042 (0.000098)	0.67
2 Years–1 year	Medial tibia	Medial tibia	0.000053 (0.000105)	0.61	0.000088 (0.000123)	0.48
	Medial tibia	Central medial femur	0.000147 (0.000130)	0.26	0.000113 (0.000155)	0.47
1 Year–baseline	Central medial femur	Medial tibia	0.000149 (0.000122)	0.22	0.000132 (0.000130)	0.31
	Central medial femur	Central medial femur	0.000027 (0.000145)	0.85	−0.000090 (0.000142)	0.53
2 Year–1 year	Central medial femur	Medial tibia	−0.000178 (0.000155)	0.25	−0.000062 (0.000161)	0.70
	Central medial femur	Central medial femur	0.000274 (0.000196)	0.17	0.000237 (0.000212)	0.27

*Adjusted for age, body mass index, knee malalignment and the Kellgren and Lawrence grade.

†Statistical significance defined as $p < 0.05$.

‡decreased group, dGEMRIC index lower at 1 year than at baseline; increased group, dGEMRIC index higher at 1 year than at baseline. dGEMRIC, delayed gadolinium-enhanced MRI of cartilage.

mean T2 values than knees with no changes in cartilage morphology scores. However, Eckstein *et al*¹² found no significant association between baseline cartilage matrix alterations on both T2 and dGEMRIC and cartilage thickness loss over 2 years, after correction for multiple testing.

Our study considered the association of changes over time in the cartilage matrix of specific regions in the medial tibiofemoral compartment as assessed by dGEMRIC, with changes in quantitatively assessed cartilage thickness in the same regions. One would assume that a decrease in dGEMRIC indices in a given region, corresponding to a decrease in the GAG concentration of the cartilage matrix, would be associated with morphological chondral changes, more likely with cartilage loss in the same region. Surprisingly, we found that a decrease in dGEMRIC indices was significantly associated with an increase in cartilage thickness.

Our results should be interpreted carefully: the relationship was only shown in knees without OA (KL grades 0 and 1) and in knees with early radiographic OA (KL grade 2) in our first analysis, with a relatively short follow-up. We may hypothesise that the decrease in dGEMRIC indices seen over the first year represents very early degeneration of the cartilage matrix, possibly associated with swelling and softening of the articular cartilage^{29–30} that occurs before cartilage loss is detected and which would increase cartilage thickness on MRI. It is also likely that such an association, demonstrated again in our second analysis of the whole sample, can be linked to knees without radiographic OA or with early radiographic OA (82.4% of the whole sample; $N=122$). Supporting our hypothesis, previous studies have demonstrated that cartilage may be thicker in specific sub-regions of tibiofemoral compartments in knees with pre-radiographic OA and in early stages of OA.^{31–33} Furthermore, a study conducted by Chen *et al*³⁴ showed that histological features of early cartilage degeneration including corruption of cartilage matrix fibrillar architecture correlated with the swelling potential of cartilage.

Our study demonstrated that thickening of cartilage over time was associated with a decrease in cartilage GAG concentration as measured by dGEMRIC in some regions of the medial compartments of pre-radiographic and early radiographic OA knees. This association also supports the suggestion that cartilage thickening may occur in early stages of the disease. Although dGEMRIC demonstrates potential to detect early degenerative alterations in the cartilage matrix, the technique is difficult to implement in routine clinical practice because it is invasive (need for intravenous contrast administration) and time consuming.

Some limitations to our study need mentioning. First, it is not known how low the dGEMRIC index needs to be in a given region of the knee at baseline for future cartilage loss to occur. It is possible that a decrease in the dGEMRIC index from a relatively high baseline index might not be sufficient to predict cartilage loss. Second, we considered any decrease or increase in absolute dGEMRIC indices as ‘change’ in dGEMRIC and very small changes may not be sufficient to predict cartilage loss. Third, our data cover a relatively short time of only 2 years. The associations we found might change if the intervals between assessments of dGEMRIC and cartilage thickness were longer. Fourth, we had no arthroscopic or surgical data to confirm that softening and swelling of cartilage occurred. Fifth, our sample comprised only middle-aged women and our results might not apply to men or young, athletic subjects. Finally, we assessed medial tibiofemoral cartilage morphology quantitatively, which is very sensitive to changes in thickness and volume,¹³ but is less sensitive to small focal cartilage defects. We might have missed some incidence or progression of small focal cartilage defects, especially in the knees with KL grades 0–2.^{35–36}

In conclusion, we showed that a decrease in dGEMRIC indices was associated with an increase in cartilage thickness in the medial tibiofemoral compartment, mainly in knees without radiographic OA or with early radiographic OA, over a 2-year period. The association might be related to swelling and softening of the medial tibiofemoral cartilage, where a decrease in the

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GAG concentration can be found in very early stages of cartilage degeneration. Such knowledge is of utmost importance for monitoring cartilage thickness in clinical trials. Ideally, morphological and compositional techniques should be combined to monitor cartilage status over time.

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Acknowledgements We thank the participants and staff of the Pfizer A9001140 Osteoarthritis Study. We are grateful to the dedicated group of study coordinators whose skills were essential in assuring the successful conduct of this study: Manal Al-Suqi, Emily Brown, Janie Burchett, Sandra Chapman, Wandra Davis, Eugene Dunkle, Susan Federmann, Kristen Fredley, Donna Gilmore, Joyce Goggins, Sasha Goldberg, Norine Hall, Robert P Marquis, Thelma Munoz, Bruce Niles, Scott Squires and Kim Tally. We also thank the staff at Chondrometrics: Gudrun Goldmann, Linda Jakobi, Manuela Kunz, Dr Susanne Maschek, Sabine Mühlisier, Annette Thebis and Barbara Wehr. We thank the dedicated MRI technologists, the Duke Image Analysis Laboratory staff: Maureen Ainslie, Cecil Charles, April Davis, Allison Fowlkes, Mark Ward and Scott White; the Pfizer A9001140 Team: Lydia Brunstetter, Peggy Coyle, Yevgenia Davidoff, Charles Packard, Ann Remmers, Mark Tengowski, Jeff Evelhoch (now Merck, Darmstadt, Germany) and John Kotyk (now Washington University, St Louis, Michigan, USA). Kenneth Brandt is also thanked for adjudicating on the radiographic readings. We also thank all the A9001140 site investigators: Julia Crim, Gary Hutchins, Chris Jackson, Virginia Byers Kraus, Nancy Lane, Thomas M Link, Sharmila Majumdar, Steve Mazzuca, Prasad Pottumarthi, Thomas Schnitzer, Mihra Taljanovic and Berchman Vaz. Finally, we thank all the staff of the participant institutions at which the MRIs were obtained: (1) University of Arizona (Department of Radiology), Tucson, Arizona, USA; (2) University of California at San Francisco (Department of Radiology), San Francisco, California, USA; (3) Beth Israel Deaconess Medical Center, Harvard Medical School (Department of Radiology), Boston, Massachusetts, USA; (4) Evanston Northwestern Healthcare (Department of Radiology), Evanston, Illinois, USA; (5) Duke Image Analysis Laboratory, Durham, North Carolina, USA; (6) University of Utah (School of Medicine), Salt Lake City, Utah, USA; (7) Indiana University School of Medicine (Department of Radiology), Indianapolis, Indiana, USA.

Contributors Conception and design, drafting of the article, critical revision of the article for important intellectual content, final approval of the article: all authors. Analysis and interpretation of the data: MDC, DB, FE, LL and AG. Provision of study materials or patients: DJH and MPHGL. Statistical expertise: DJH and LL.

Funding This work was supported by Pfizer Inc.

Competing interests Michel D. Crema is shareholder and VP Musculoskeletal of Boston Imaging Core Lab (BICL), LLC. David J. Hunter receives grant support from Pfizer, Merck and DonJoy. Deborah Burstein receives grant support from Pfizer, Stryker, Gelita and Genzyme. Frank W. Roemer is shareholder and CMO of BICL, LLC. Felix Eckstein is CEO and co-owner of Chondrometrics GmbH. He provides consulting services to MerckSerono, Novartis and Sanofi Aventis. Marie-Pierre Hellio Le-Graverand is employed by Pfizer Inc. Ali Guermazi is President of BICL, LLC. He also provides consulting services for MerckSerono, Genzyme, Novartis, Stryker, and AstraZeneca.

Ethics approval The study was conducted in compliance with local institutional review boards, informed consent regulations, the International Conference on Harmonization Good Clinical Practices Guidelines, and the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

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Association of changes in delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) with changes in cartilage thickness in the medial tibiofemoral compartment of the knee: a 2 year follow-up study using 3.0 T MRI

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Ann Rheum Dis 2014 73: 1935-1941 originally published online July 19, 2013
doi: 10.1136/annrheumdis-2012-203083

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