Image registration improves human knee cartilage T1 mapping with delayed gadolinium-enhanced MRI of cartilage (dGEMRIC)

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Abstract

Objectives To evaluate the effect of automated registration in delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) of the knee on the occurrence of movement artefacts on the T1 map and the reproducibility of region-of-interest (ROI)-based measurements.

Methods Eleven patients with early-stage knee osteoarthritis and ten healthy controls underwent dGEMRIC twice at 3 T. Controls underwent unenhanced imaging. ROIs were manually drawn on the femoral and tibial cartilage. T1 calculation was performed with and without registration of the T1-weighted images. Automated three-dimensional rigid registration was performed on the femur and tibia cartilage separately. Registration quality was evaluated using the square root Cramér–Rao lower bound (CRLB_σ). Additionally, the reproducibility of dGEMRIC was assessed by comparing automated registration with manual slice-matching. **Results** Automated registration of the T1-weighted images improved the T1 maps as the 90% percentile of the CRLB_σ was significantly ($P < 0.05$) reduced with a median reduction of 55.8 ms (patients) and 112.9 ms (controls). Manual matching and automated registration of the re-imaged T1 map gave comparable intraclass correlation coefficients of respectively 0.89/0.90 (patients) and 0.85/0.85 (controls). **Conclusions** Registration in dGEMRIC reduces movement artefacts on T1 maps and provides a good alternative to manual slice-matching in longitudinal studies.

Key Points

- Quantitative MRI is increasingly used for biomedical assessment of knee articular cartilage
- Image registration leads to more accurate quantification of cartilage quality and damage
- Movement artefacts in delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) are reduced
- Automated image registration successfully aligns baseline and follow-up dGEMRIC examinations
- Reproducibility of dGEMRIC with registration is similar to that using manual slice-matching

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Keywords Magnetic resonance imaging · Articular cartilage · Knee osteoarthritis · Computer-assisted image processing · Reproducibility of results

Abbreviations and acronyms

CRLB	Cramér–Rao lower bound
CRLB_σ	Square root of the Cramér–Rao lower bound
90%- CRLB_σ	90% percentile of the CRLB_σ in a region of interest
CV	Coefficient of variation
dGEMRIC	Delayed gadolinium-enhanced MRI of cartilage
FSPGR	Fast spoiled gradient-recalled echo
VGA	Visual grading analysis

Introduction

Osteoarthritis, the most common form of arthritis, is characterised by the degradation and loss of cartilage [1]. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) has been introduced as a non-invasive quantitative technique to measure cartilage quality by evaluating its glycosaminoglycan content [2–4]. Imaging is performed after administration of a negatively charged contrast agent that diffuses into cartilage in reverse relationship to the charge of glycosaminoglycan molecules. A quantitative T1 map is reconstructed from images acquired consecutively with different inversion times (TIs).

Automated image registration may improve dGEMRIC studies in two ways. First, T1 map quality may be improved by registration of the T1-weighted images to correct for patient movement during the acquisition process. Only a few papers on dGEMRIC used image registration to correct for motion artefacts [5, 6]. Moreover, registration of the T1-weighted images has not been evaluated before in patients with knee osteoarthritis. Second, automated image registration can be applied in longitudinal studies to compare T1 maps acquired at different time points. Previous studies did not use registration for this purpose, but instead relied on manual matching of slices [7, 8], which is operator-dependent and time-consuming. Automated image registration eliminates the subjective manual slice-matching and manually outlined ROIs are required only once. This can be of value in follow-up studies evaluating for example the effect of a treatment.

The present study evaluates the effects of both image registration steps on the outcome of dGEMRIC in patients with knee osteoarthritis as well as in healthy controls.

Materials and methods

Subjects

This study was approved by the institutional review board of Erasmus MC, Rotterdam, The Netherlands. Informed consent was obtained from all subjects.

Two subject groups were included in this study. Group I consisted of 11 patients (age 52.2 ± 11.0 years, seven male) with early-stage knee osteoarthritis (knee complaints >3 months, visual analogue pain scale >20 mm and Kellgren–Lawrence grade I or II on radiography [9]). Group II consisted of ten healthy controls (age 26.7 ± 8.6 years, four male).

Imaging protocol

Images were acquired on a 3-T MRI (Discovery MR750; General Electric Healthcare, Milwaukee, WI, USA). The three-dimensional (3D) protocol for T1-weighted imaging consisted of an inversion recovery fast spoiled gradient-recalled echo (FSPGR) sequence with five TIs (100; 200; 400; 800; 2,100 ms) [10]. The repetition time (TR) was the inversion time plus the time after read-out (TS=3.9 ms). Other parameters were: flip angle = 15° , echo time = 1.5 ms, field of view = 15×15 cm, slice thickness = 3 mm, slice spacing = 3 mm, in-plane voxel size = 0.6×0.6 mm, number of slices in the sagittal plane = 36. The dGEMRIC MR protocol lasted approximately 15 min.

In patients, the dGEMRIC protocol [10] was performed twice with an interval of 7 days (range 5–14 days). A double dose (0.2 mmol/kg) of Magnevist (Bayer, Berlin, Germany) was injected intravenously. Next, the patients were asked to cycle for 10 min on a home trainer to promote contrast agent distribution into and throughout the knee and the cartilage [11]. After cycling, there was a delay of 80 min before the participants underwent MRI. An open design three-channel knee coil (Flick Engineering Solutions, Winterswijk, The Netherlands) was used, which enabled imaging of patients with a large knee diameter. Controls underwent MRI with the standard eight-channel knee coil (General Electric Healthcare) requiring a knee diameter less than 14 cm. For the controls, no contrast agent was used, and the second MR examination was acquired after a short break and repositioning of the knee.

Definition of regions of interest

For each subject, two regions of interest (ROIs) on the femoral and tibial cartilage were outlined by a trained researcher with a medical degree (J.v.T.). The femoral cartilage

ROI consisted of the adjacent trochlear, weight-bearing and posterior cartilage of the femur, and the tibial cartilage ROI consisted of the weight-bearing tibial plateau cartilage. The ROI outlining was performed on the central slice through the medial and lateral tibiofemoral joint, for both the first and second MR examination, resulting in eight cartilage ROIs per subject.

T1 calculation and uncertainty estimate

The T1 map was reconstructed by voxelwise fitting of the relationship $SI(TI) = S_0 \cdot (1 - A \cdot \exp(-TI/T1) + \exp(-TR/T1))$ [10] to the T1-weighted images acquired at a range of inversion times. The fitting was performed with a maximum likelihood estimator of T1, S_0 (fully relaxed signal) and A (inversion efficiency), which takes into account the Rician distribution of the data because, for magnitude MR images, this is more accurate than the commonly used normal distribution [12].

The uncertainty of the estimated parameters at each voxel can be expressed by the Cramér–Rao lower bound (CRLB), which gives a lower bound for the variance [12–14]. The square root of the T1 CRLB ($CRLB_{\sigma}$) can therefore be interpreted as a lower bound for the standard deviation of the T1 value, which quantifies how noise on the MR signal propagates to uncertainty of the estimated T1 value. In quantitative MRI, $CRLB_{\sigma}$ has previously been used for optimisation of MR sequences [15–17], but it can also be used as an indicator of misalignment. Misalignment of the T1-weighted images, especially at tissue boundaries, results in biologically implausible values of S_0 , A and T1, often associated with a high uncertainty, which is expressed by $CRLB_{\sigma}$. The T1 calculations were performed using in-house developed Matlab software (R2008a; The MathWorks, Natick, MA, USA), which produces both the T1 map and the $CRLB_{\sigma}$ map. As a summary statistic for the $CRLB_{\sigma}$ values, we computed the 90% percentile (90%- $CRLB_{\sigma}$) over all voxels in each annotated ROI; the lower this value, the better. We also computed the 90%- $CRLB_{\sigma}$ over all voxels in all ROIs together, to obtain a single measure per subject.

Registration of T1-weighted images

All T1-weighted images were registered in 3D with respect to that T1-weighted image showing the highest contrast between cartilage and surrounding synovial fluid, and between cartilage and bone cortex (FSPGR_{TI=2,100}). Registrations were performed using Elastix software [18] using a rigid transformation model (translations and rotations). Femoral and tibial regions were registered separately based on subvolumes

containing only the specific bone and surrounding tissue to allow correction for motion of the knee joint (Fig. 1). The registration was optimised over 1,000 iterations with localised mutual information (LMI) as a similarity measure [19]. Per iteration, LMI was calculated using 2,048 random samples obtained from a sample region of size $50 \times 50 \times 50$ mm. Cubic B-spline interpolation was used when applying the deformation to the moving image. The exact registration settings can be found on the parameter file database on the Elastix website: <http://elastix.isi.uu.nl/wiki.php>.

T1 maps were calculated with and without registration. A Wilcoxon signed rank test was used to test for a significant effect of registration on the 90%- $CRLB_{\sigma}$ values.

Registration between the first and second MR examinations

To align the FSPGR_{TI=2,100} images from the first and second MR examinations, registration was performed with the same method as in the previous section. Based on this registration, the T1 maps from the second MR examination were transformed to the T1 maps obtained in the initial study. The result of this alignment was compared with the reference standard of manually selecting matching slices, which was performed by a trained researcher (J.vT.) visually inspecting FSPGR_{TI=2,100} images from the first and second MR examinations for matching slices.

Analysis of the reproducibility between the first and second MR examinations was based on correlations of a weighted mean T1 value per ROI. A weighted mean was computed to reduce the effect of outliers which are, for example, caused by bone voxels accidentally included in the

Fig. 1 Registration is performed separately on the femoral (red) and tibial (blue) subvolumes to correct for motion of the knee joint. The background greyscale image is a T1-weighted image (FSPGR_{TI=2,100})

cartilage ROIs. As outliers are expected to have a high CRLB_σ , the reciprocal of the CRLB_σ was used as the weight of each voxel to reduce their effect.

The reproducibility of the weighted mean T1 values was assessed using the intraclass correlation coefficient (ICC), Pearson's correlation coefficient and total least squares regression. In these analyses we treated the four ROIs on each image as independent measurements. The ICC describes the resemblance of two sets of data with identical units and an equal variance [20, 21], and can therefore be used to measure the agreement between the first and the registered second MR examination. A total least squares fit [22, 23] was performed to estimate a linear relation between measurements obtained at the two examinations. A fit with a slope significantly different from 1 would imply a systematic difference.

Results

Registration of T1-weighted images

Registration of the T1-weighted images improved the T1 mapping, as CRLB_σ was reduced and the homogeneity of the T1 maps was increased (Fig. 2). Visual inspection of all

ROIs showed an improvement in the alignment of the T1-weighted images due to registration. This effect was similar in the femoral and tibial cartilage ROIs. In only three out of 84 tibial cartilage ROIs, the severity of movement artefacts was increased by registration, which was caused by misalignment of the $\text{FSGPR}_{\text{TI}=100}$ image in two of the cases.

Table 1 reports per subject the 90%- CRLB_σ over all voxels in the eight ROIs, with and without registration. Table 2 shows the statistics for these measurements (*first row*) and for each ROI separately (*rows 2–9*). The 90%- CRLB_σ decreased significantly in patients ($P=0.003$) and controls ($P=0.005$) owing to automated registration. The effect of registration was more pronounced in the femoral cartilage than in the tibial cartilage. With a Bonferroni correction for multiple testing, the registration effect in the femoral ROIs was still significant ($P<0.05$).

Registration between the first and second MR examinations

Figure 3 shows scatter plots of the weighted mean T1 measurements on the first versus second MR examination. Table 3 summarises the statistics. In patients, the ICC for the manual slice-matching was 0.89 and with registration similar results were obtained (ICC=0.90). In controls, an ICC of 0.85 was

Fig. 2 Comparison of T1 map and square root of CRLB_σ map of a patient with and without automated registration to correct for patient movement (colour overlay). The CRLB_σ (ms) provides a lower bound for standard deviation of T1 (ms) and is a measure for registration quality. The background grey-scale image is a T1-weighted image ($\text{FSPGR}_{\text{TI}=2,100}$). **a** T1 map without registration, **(b)** CRLB_σ map without registration showing high uncertainty in the T1 estimates, **(c)** improved T1 map with registration, **(d)** CRLB_σ map with registration showing reduced uncertainty in the T1 estimates

Table 1 The 90%-CRLB_σ calculated over all voxels in the eight cartilage ROIs

Subject	Patients		Controls	
	No registration	Automated registration	No registration	Automated registration
1	1,753	177	260	244
2	43	34	> 10,000	605
3	142	84	443	298
4	96	74	410	360
5	765	152	176	164
6	178	120	> 10,000	712
7	111	74	456	385
8	> 10,000	762	441	267
9	128	105	> 10,000	2,609
10	152	86	165	141
11	91	69	-	-

In one patient and three control subjects the 90%-CRLB_σ value without registration is over 10,000 ms. This resulted from voxels where the maximum likelihood fit indicated an ‘infinitely’ long T1 time

found with both manual matching and registration. These ICC values indicate a similar reproducibility for both methods as the ICC values lie in each other’s 95% confidence interval. The Pearson correlation coefficients show the same pattern. Linear total least squares regression resulted in a slope of approximately 1 in patients and controls, with both manual matching and automated registration, which confirms that there are no systematic differences.

Discussion

Our study demonstrates that automated registration can improve two aspects of dGEMRIC studies in the setting of knee

osteoarthritis: the T1 map calculation and the reproducibility of T1 maps obtained at different MR examinations.

First, applying automated image registration in the calculation of T1 maps from T1-weighted images improves the T1 maps and reduces the uncertainty in the estimated T1 value. In finger and hand arthritis, analysis by the coefficient of variation (CV) and visual grading analysis (VGA) showed that registration improves image quality and reduces variability [5]. In knee dGEMRIC, this has only been investigated in five healthy volunteers [6] where the goodness of the T1 fit was evaluated using χ^2 analysis. In our paper the CRLB_σ was used to measure the effect of registration on the T1 map. Like χ^2 analysis, CRLB_σ provides a quantitative measure to express the quality of the T1 fit, which is not provided by CV or VGA. However, χ^2 and CRLB_σ express different properties of the quality of fit: χ^2 quantifies the difference between the fit and the measurements, and CRLB_σ quantifies how noise on the MR signal propagates to the fit. CRLB_σ has the advantage over χ^2 of being an absolute measure expressed in the same units (ms) as T1. The results of our study show a reduction of CRLB_σ due to registration, with a more pronounced effect in the femoral cartilage than in tibial cartilage. The 90%-CRLB_σ did not show a significant effect of registration on the tibial ROIs (Table 2). This may be explained by the smaller signal intensity difference between cartilage and bone observed in the tibia compared with the femur. Misalignments in the tibial area will therefore have less effect on the CRLB_σ than misalignments in the femoral region.

Second, automated image registration in evaluation of dGEMRIC reproducibility has been addressed. Using manual slice-matching, Multanen et al. [7] reported an ICC of 0.95 in femoral cartilage and 0.87 in tibial cartilage of control subjects and Siversson et al. [8] found a femur ICC of approximately 0.68 in patients. We found an ICC of 0.89 with the manual slice-matching method in patients.

Table 2 The effect of registration on the 90%-CRLB_σ of all voxels in the eight ROIs combined and of each ROI separately

ROI	Patients (n=11)		Controls (n=10)	
	Median difference ^a	P value ^b	Median difference	P value
All voxels in the eight ROIs	55.8	0.003	112.9	0.005
Femoral cartilage in the selected slice in the lateral compartment: Initial MRI	71.6	0.004	1,561.6	0.005
Femoral cartilage in the selected slice in the medial compartment: Initial MRI	223.2	0.003	210.9	0.005
Lateral femoral cartilage on second MRI	73.8	0.003	677.6	0.005
Medial femoral cartilage on second MRI	104.8	0.003	72.8	0.009
Tibial cartilage in the selected slice in the lateral compartment: Initial MRI	-5.7	0.374	-63.1	0.647
Tibial cartilage in the selected slice in the medial compartment: Initial MRI	-7.4	0.350	-5.1	0.508
Lateral tibial cartilage on second MRI	3.0	0.424	-45.0	0.959
Medial tibial cartilage on second MRI	-15.4	0.286	148.6	0.037

^aDifferences in the median of the 90%-CRLB_σ for all subjects between no registration and automated registration

^bP values of the Wilcoxon signed rank test

Fig. 3 Weighted mean T1 value per ROI for all patients (**a, b**) and controls (**c, d**). Subjects are represented by different coloured markers. The weighted means of the T1 maps from the first and second MR examinations are plotted against each other with manual slice-matching (**a, c**) and automated registration (**b, d**). The *black line*

represents $y=x$, which is the expected result at perfect registration and reproducibility; the *blue line* is a linear total least squares fit through the points; r represents the Pearson's correlation coefficient of the points and ICC the intraclass correlation coefficient

For the control group, the manual approach resulted in an ICC of 0.85, which is comparable to the aforementioned studies. The automated registration method presented in our study requires only one manually drawn cartilage mask for evaluating the same ROI in two or more MR examinations. Therefore, analysis of dGEMRIC is less time-consuming using the automated registration method. The actual amount of time that can be saved depends on the number of ROIs,

slices and MR examinations to be analysed. This is particularly of interest if two or more MR examinations need to be analysed for large cohorts of patients. Automated registration yielded similar results to the manual method ($ICC=0.90$ in patients and 0.85 in controls). The reproducibility in patients was slightly higher than in controls, which could be explained by differences in signal-to-noise ratio (SNR) owing to different coils, or by the difference in T1 values as

Table 3 Comparison between first and second MR examinations: weighted mean T1 values of each ROI with manual slice-matching and automated registration

	Patients		Controls	
	Manual matching	Registration	Manual matching	Registration
$ICC(2,1)$ (CI)	0.893 (0.813–0.940)	0.902 (0.827–0.945)	0.849 (0.732–0.917)	0.851 (0.736–0.919)
r (CI)	0.892 (0.809–0.940)	0.901 (0.824–0.945)	0.855 (0.742–0.921)	0.858 (0.745–0.923)
slope (CI)	1.030 (0.412–1.649)	1.036 (0.383–1.688)	1.044 (0.589–1.499)	1.065 (0.506–1.624)

$ICC(2,1)$ two-way random intraclass correlation coefficient based on single measures, r Pearson's correlation coefficient, *slope* the slope obtained with a total least squares fit, *CI* 95% confidence interval

controls underwent unenhanced MR imaging. The SNR was actually higher in controls than in patients (132 ± 38 vs 67 ± 37), so the better reproducibility in patients is most likely explained by the presence of contrast agent leading to shorter T1 values. The range of inversion times in the FSPGR sequence is optimised for these typical T1 values in the presence of contrast agent. The lower 90%-CRLB_σ values for patients reflect this (Table 1).

Although this paper focuses on dGEMRIC, the registration method used is not specifically developed for dGEMRIC. The method should therefore be applicable to other MR mapping methods as well, such as T1ρ and T2.

In conclusion, automated registration of dGEMRIC in knee cartilage improves the quality of T1 maps and provides a good alternative to manual slice-matching in longitudinal studies as it leads to equal reproducibility and is operator-independent.

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