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SCIENTIFIC ARTICLE

Cartilage quality in rheumatoid arthritis: comparison of T2* mapping, native T1 mapping, dGEMRIC, ΔR1 and value of pre-contrast imaging

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Abstract
Purpose To prospectively evaluate four non-invasive markers of cartilage quality—T2* mapping, native T1 mapping, dGEMRIC and ΔR1—in healthy volunteers and rheumatoid arthritis (RA) patients.
Materials and methods Cartilage of metacarpophalangeal (MCP) joints II were imaged in 28 consecutive subjects: 12 healthy volunteers [9 women, mean (SD) age 52.67 (9.75) years, range 30–66] and 16 RA patients with MCP II involvement [12 women, mean (SD) age 58.06 (12.88) years, range 35–76]. Sagittal T2* mapping was performed with a multi-echo gradient-echo on a 3 T MRI scanner. For T1 mapping the dual flip angle method was applied prior to native T1 mapping and 40 min after gadolinium application (delayed gadolinium-enhanced MRI of cartilage, dGEMRIC, $T1_{Gd}$). The difference in the longitudinal relaxation rate induced by gadolinium (ΔR1) was calculated. The area under the receiver operating characteristic curve (AROC) was used to test for differentiation of RA patients from healthy volunteers.
Results dGEMRIC (AUC 0.81) and ΔR1 (AUC 0.75) significantly differentiated RA patients from controls. T2* mapping (AUC 0.66) and native T1 mapping (AUC 0.66) were not significantly different in RA patients compared to controls.
Conclusions The data support the use of dGEMRIC for the assessment of MCP joint cartilage quality in RA. T2* and native T1 mapping are of low diagnostic value. Pre-contrast T1 mapping for the calculation of ΔR1 does not increase the diagnostic value of dGEMRIC.

Keywords MRI · T2* mapping · Cartilage · Rheumatoid arthritis · dGEMRIC · T1 mapping

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Introduction

Cartilage degradation has been recognized as a key feature of joint damage in rheumatoid arthritis (RA) [1]. T2*

mapping, native T1 mapping and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) have been used for non-invasive assessment of cartilage quality.

T2* mapping is a non-invasive measure of cartilage quality reflecting cartilage hydration and collagen integrity [2–4]. T2* mapping has been demonstrated to be sensitive to cartilage damage in osteochondrosis dissecans of the talus [5] and in femoroacetabular impingement of the hip [6].

dGEMRIC uses the ionic properties of the contrast agent $Gd(DTPA)^{2-}$ for molecular imaging. In cartilage with reduced density of negatively charged glycosaminoglycan (GAG), a main component of hyaline cartilage, the penetration of $Gd(DTPA)^{2-}$ is increased. This way, the concentration of contrast agent in cartilage is a measure of GAG content [7] and can be assessed with $T1_{Gd}$ mapping [8].

Assuming that $T1_{Gd}$ after $Gd(DTPA)^{2-}$ administration corresponds to GAG content, one implicitly assumes that pre-contrast T1 relaxation time is constant. However, pre-contrast T1 values have been reported to be abnormal in damaged cartilage in vitro [9] and in vivo [10]. In particular, cartilage fibrillation and cartilage edema have been associated with an increase in pre-contrast T1 values [9, 10]. In the follow-up of surgical cartilage repair procedures, pre-contrast T1 values have been reported to be severely altered [11, 12]. For this reason, ΔR1 (the difference in relaxation rate between pre- and post-contrast T1 mapping) has been proposed as a more precise parameter of Gd-$DTPA^{2-}$ concentration in cartilage [10, 11, 13]

Operationally, it is desirable to perform dGEMRIC without the acquisition of pre-contrast images because the long waiting time (typically 30–90 min [8]) after contrast injection implies two consecutive imaging sessions for the patient. In a clinical study ΔR1 has been demonstrated to be only slightly superior to post-contrast $T1_{Gd}$ mapping in differentiating healthy volunteers from knee osteoarthritis (OA) patients [14]. In early hip OA, ΔR1 and post-contrast $T1_{Gd}$ (i.e. dGEMRIC) have been shown to correlate in a linear manner [15]. Both studies suggest post-contrast $T1_{Gd}$ may be sufficient for the evaluation of cartilage damage in clinical dGEMRIC studies of OA.

Recently dGEMRIC has been used to assess cartilage quality in finger joints of patients with RA, demonstrating significant differences compared to healthy controls [16]. No reports exist on the value of pre-contrast T1 mapping in dGEMRIC either in finger joints or in RA patients.

The purpose of the present study was to prospectively evaluate four non-invasive markers of cartilage quality—T2* mapping, native T1 mapping, dGEMRIC and ΔR1—in healthy volunteers and rheumatoid arthritis (RA) patients.

Materials and methods

Patients

This study was approved by the institutional review board and all patients and volunteers provided written informed consent.

A total of 28 consecutive subjects were enrolled in the present study: 12 healthy volunteers [9 women, mean (SD) age 52.7 (9.8) years, range 30–66] and 16 patients [12 women, mean (SD) age 58.1 (12.9) years, range 35–76] with established RA according to the 2010 ACR criteria [17] were imaged (Table 1). Inclusion criteria were MCP II involvement without visual cartilage loss in MRI. Signs of inflammation [joint swelling, pain and tenderness as well as Disease Activity Score 28 (DAS 28)] were recorded in clinical examination. CRP was determined within 5 days of MRI examination.

Imaging protocol

Images of MCP II were acquired on a 3 T MR scanner (Magnetom Trio, Siemens, Erlangen, Germany). The subjects were positioned prone with the hand extended overhead, palm down. One 4 cm loop coil was fixed on the palmar, and another coil on the dorsal side of MCP II.

Sagittal T2* mapping was performed with a multi-echo gradient echo sequence with a matrix of 384 × 312 , FOV 90 mm allowing for an in-plane resolution of 234 μm, a slice thickness of 2 mm, a TR of 600 ms and a train of five TEs (5.68, 15.82, 25.96, 36.10, 46.24 ms). Two averages were chosen, the bandwidth was 260 Hz/pixel and flip angle was 60°. Acquisition time was 3:47 min. T2* maps were calculated in-line with a pixel-wise monoexponential non-negative least squares fit analysis using MapIt software (Siemens, Erlangen, Germany).

For T1 mapping, the dual flip angle technique was applied [18]. T1 mapping was performed prior to intravenous administration of 0.4 ml/kg body weight of gadolinium contrast agent (Magnevist; Schering, Berlin, Germany) and after a 40 min delay (dGEMRIC, $T1_{Gd}$). TE was 3.72 ms, TR was 15 ms, flip angles were 5° and 26°, slice thickness was 2 mm and the FOV was 73 × 90 mm with a matrix of 312 × 384 and an in-plane resolution of 234 μm.

Table 1 Study population

	Healthy controls	Rheumatoid arthritis patients	*P*
Number	13	16	
Male/female (*n*)	3/9	4/12	1.00
Mean age (range)	52.7 (30–66)	58.1 (35–76)	0.24

Acquisition time was 2:25 min. Slices were positioned perpendicular to the joint spaces.

Image processing

The image data of the dGEMRIC measurements were transferred to an external workstation running Windows XP® (Microsoft®, Redmond, WA). T1 maps were corrected for patient movement between measurements with the STROKE-TOOL software (http://www.digitalimagesolutions.de, Frechen, Germany) using an image registration method based on least squares measure [19].

T1 maps were generated from the native images (T1 map) and the gadolinium-enhanced images ($T1_{Gd}$, i.e. dGEMRIC). The T1 maps were calculated according to Eq. 1:

$$T_1(x,y,z) = \frac{TR}{\ln\left[\frac{\sin(\alpha_1)\cos(\alpha_2) - Q(x,y,z)\sin(\alpha_2)\cos(\alpha_1)}{\sin(\alpha_1) - Q(x,y,z)\sin(\alpha_2)}\right]} \quad (1)$$

where $Q(x,y,z) = \frac{S_1(x,y,z)}{S_2(x,y,z)}$ and $S_1(x,y,z)$, $S_2(x,y,z)$ are the pixel intensities in the images acquired with flip angles of 5° and 26°.

Image analysis

Cartilage thickness was measured including phalangeal and metacarpal cartilage in the same image section.

ROIs were selected to include the phalangeal and the metacarpal cartilage of MCP II in the same image section (Fig. 1). Mean T2*, native T1 values and $T1_{Gd}$ values were determined. To take into account the different sizes of the phalangeal and the metacarpal cartilage, weighted means of the two areas were calculated using the number of pixels as weights. ΔR1 was calculated with Eq. 2:

$$\Delta R1 = 1/T1_{Gd} - -1/T1 \quad (2)$$

Statistical analysis

Student's independent two-sample *t*-test was applied to determine if healthy subjects and RA patients differed significantly in their means for each of the four investigated parameters.

The area under the receiver operating characteristic curve (AROC) was used to reveal the parameter which is best qualified to identify RA patients. To determine the best cut off points to distinguish between RA patients and healthy subjects, the maximum of the Youden index was calculated (Youden index = sensitivity + specificity − 1). Exact lower confidence bounds for sensitivity and specificity were computed with the binomial distribution.

Correlations among T2*, native T1, $T1_{Gd}$, ΔR1 and clinical signs of inflammation, DAS 28 and CRP were estimated with Spearman's correlation coefficient. The correlations among ΔR1, native T1 and $T1_{Gd}$ were calculated with Pearson's correlation coefficient. The statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

There was no significant differences in age (P=0.2365) and gender (P=1.0) between healthy volunteers and patients. No significant difference in MCP II cartilage thickness between the groups (healthy controls: 1.31±0.29 mm, RA patients: 1.37±0.33 mm, P=0.621) was noted.

T2* mapping

T2* values did not differ significantly between volunteers (18.79±4.49 ms) and RA patients (16.26±2.52 ms) (P=0.099) (Fig. 1, Table 2). The best cut off point to separate healthy individuals and RA patients is 19.46 according to the Youden index, which leads to a sensitivity of 0.94 with a lower confidence limit of 0.74 and a specificity of 0.58 with a lower confidence limit of 0.32 (Fig. 2, Table 2).

Native T1 mapping

No statistically significant difference between native T1 values of volunteers (958.03±90.22 ms) and RA patients (903.47±164.90 ms) (P=0.274) was noted. The best cut off point to separate healthy individuals and RA patients according to the Youden index is 864.35, which leads to a sensitivity of 0.50 with a lower confidence limit of 0.28 and a specificity of 0.92 with a lower confidence limit of 0.66 (Fig. 3).

$T1_{Gd}$ (dGEMRIC index)

There was a statistically significant difference in the means of dGEMRIC indexes between volunteers (482.55± 87.45 ms) and RA patients (367.15±95.73 ms) (P= 0.003). The best cut off point to separate healthy individuals and RA patients according to the Youden index is 378.99, resulting in a sensitivity of 0.63 with a lower confidence limit of 0.39 and a specificity of 0.92 with a lower confidence limit of 0.66 (Fig. 4). The Youden index maximises the sum of sensitivity and specificity with equal weights for sensitivity and specificity. In our case a low sensitivity would lead to a high number of RA cases

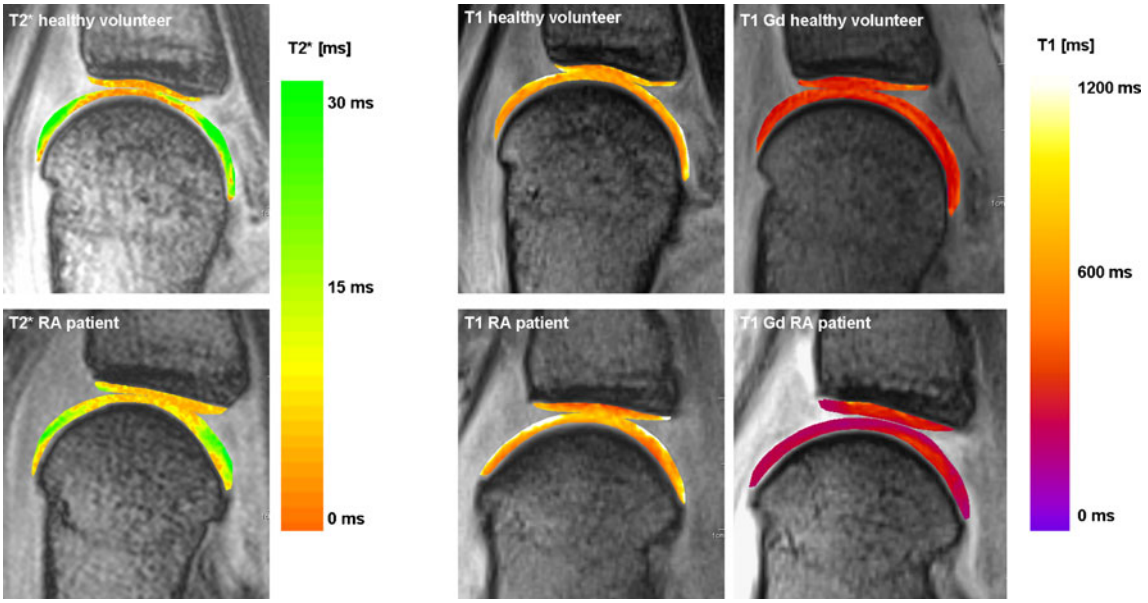

Fig. 1 T2* mapping, native T1 mapping and dGEMRIC in a healthy control and a representative RA patient. Colour maps have been superimposed on anatomical MR images

that would be diagnosed to have normal cartilage quality. If sensitivity is more important than specificity in this setting, we would rather suggest 384.33 as a cut off point, which has an only slightly lower Youden index, but leads to a sensitivity of 0.69 (lower confidence bound 0.45) and a specificity of 0.83 (lower confidence bound 0.56) (Table 3).

ΔR1

There was a statistically significant difference in the means of ΔR1 between volunteers (1.09 ±0.47 s^{-1}) and RA patients (1.78±0.93 s^{-1}) (P=0.018) (Fig. 5). The best cut off point according to the Youden index to separate healthy individuals and RA patients is 1.40 s^{-1}, which leads to a sensitivity of 0.69 with a lower confidence limit of 0.45 and a specificity of 0.75 with a lower confidence limit of 0.47.

There was a significant correlation between ΔR1 and $T1_{Gd}$ (Pearson's r=−0.92, P<0.0001) and between ΔR1 and native T1 (Pearson's r =0.41, P=0.0290) (Fig. 6).

There was no significant correlation among T2*, T1, ΔR1 or $T1_{Gd}$ and clinical signs of inflammation, DAS 28 or CRP.

Discussion

In clinical imaging and research of RA, the exploitation of the potential of MRI is continuously increasing [20–22]. Bone marrow oedema has been identified as a possible precursor to erosions and as an early marker of RA [23]. Dynamic T1-weighted imaging can be used to quantify synovial hyperperfusion reflecting arthritis activity [20, 24], and MR angiography has been shown to depict abnormal vessels reflecting synovial neovascularisation [25]. Cartilage damage in RA has been demonstrated to be associated with physical disability, suggesting that effort should be invested in research in this field [26]. Cartilage damage in RA caused by proteases is a common finding. The release of neopeptides from cartilage has been discussed to maintain the chronic immune response [27]. The depletion of GAG has been demonstrated to be a factor in in vitro studies on cartilage degeneration in RA [28]. In vivo increased levels of anti-GAG autoantibodies have been demonstrated in RA patients [29]. Increased serum levels of cartilage matrix proteins have been reported to predict radiographic joint damage [30]. In the preclinical course of RA, increased markers of cartilage turnover have been

Table 2 T2* mapping, native T1 mapping, dGEMRIC and ΔR1 of MCP II in the differentiation of RA patients from healthy volunteers

	Healthy volunteers	RA patients	P	AUC	Best cut-off
T2* (ms)	18.79±4.49	16.26±2.52	0.099	0.661	19.46
T1 (ms)	958.03±90.22	903.47±164.90	0.274	0.661	864.35
dGEMRIC index (ms)	482.55±87.45	367.15±95.73	0.003	0.813	378.99
ΔR1 (s^{-1})	1.09±0.47	1.78±0.93	0.018	0.750	1.40

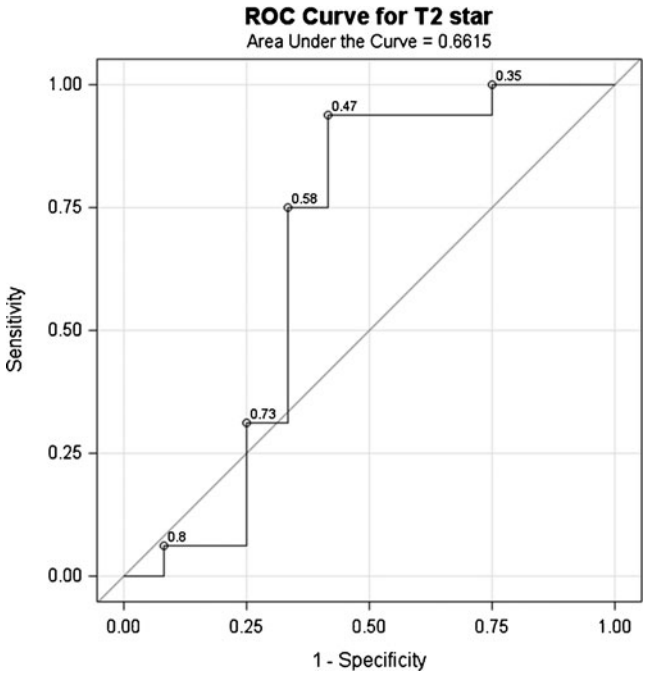

Fig. 2 Receiver operating characteristic (ROC) curve for T2*

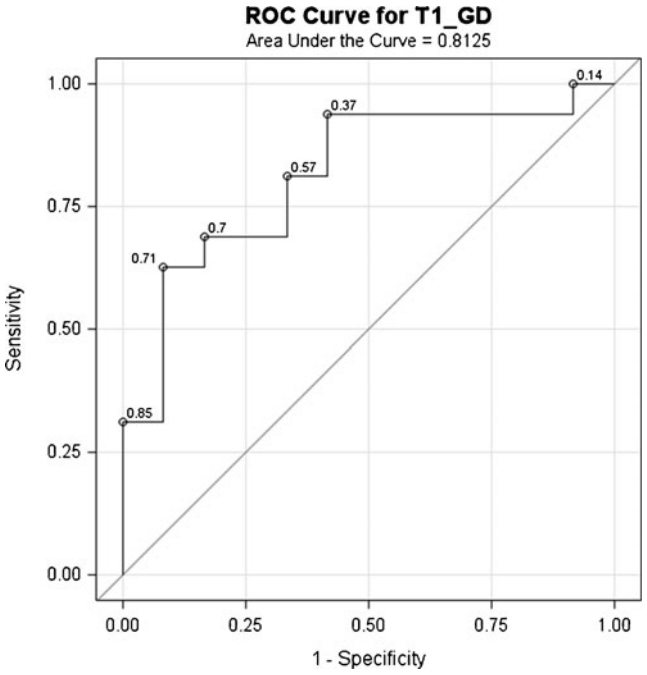

Fig. 4 Receiver operating characteristic (ROC) curve for dGEMRIC index [$T1_{Gd}$ post $Gd(DTPA)^{2-}$]

reported, suggesting that cartilage damage may be a very early feature of the disease [31]. In conventional MRI, cartilage damage is made visible as a volume loss slowly developing over years [32]. Especially in the early course of RA, cartilage loss in morphological MRI may be absent [33]. The lack of sensitivity of conventional MRI to assess cartilage damage in RA has triggered the application of molecular MRI of cartilage [16, 34]. However, to the best of our knowledge, the value of different MRI techniques sensitive to molecular cartilage damage has not been evaluated in RA patients.

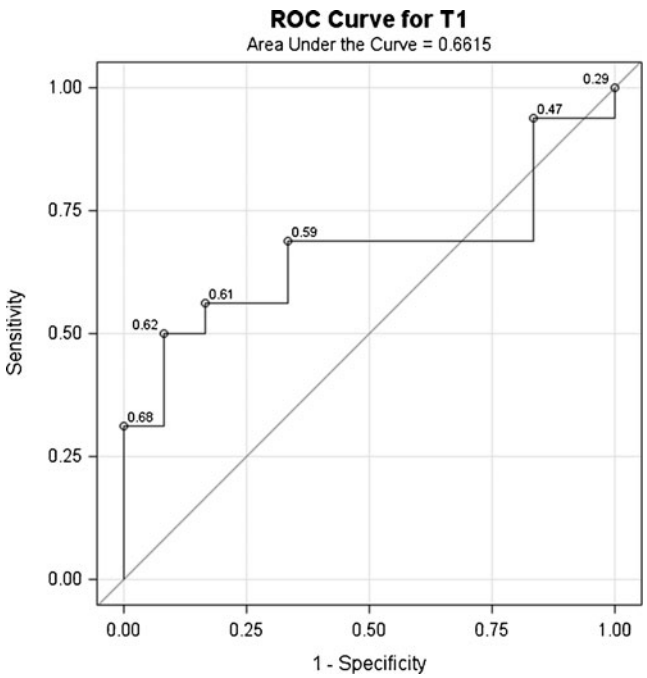

Fig. 3 Receiver operating characteristic (ROC) curve for native T1

Non-invasive measures of cartilage quality such as T2* mapping, native T1 mapping, dGEMRIC and ΔR1 may have the potential to detect cartilage damage before irreversible volume loss occurs [8]. In order to assess their possible value, the correlation of these techniques with clinical features and their discrimination of healthy control subjects from RA patients are compared in the present paper.

T2* is considered to reflect cartilage hydration and collagen integrity [5, 6]. Cartilage thinning has been proposed to lead to an increased effect of susceptibility artefacts on T2* mapping, resulting in lower T2* values [6]. A favourable technical feature of T2* mapping is that it does not require contrast agent. Gadolinium-based contrast agents are reported to induce nephrogenic systemic fibrosis (NSF) in patients with pre-existing kidney disease [35]. Furthermore, allergic-like reactions are rare but possible reactions [36]. Although NSF may be completely avoidable, if patients with renal failure are restricted from using gadolinium [37], biochemical cartilage MRI without contrast agents seems desirable. Our results indicate that no alterations can be measured with T2* mapping in finger cartilage of RA patients and that T2* mapping may be of lower diagnostic value than dGEMRIC in differentiating RA patients from controls. In our patient group, no significant cartilage thinning was noted, reducing the probability of a significantly different effect of susceptibility artefacts in this group.

Table 3 Youden index, sensitivity and specificity at different cut off values for dGEMRIC

Cut off	Sensitivity	CI_l (Se)	Specificity	CI_l (Sp)	Youden index
318.612	0.3125	0.13	1	0.78	0.312
378.990	0.6250	0.39	0.9167	0.66	0.542
384.330	0.6875	0.45	0.8333	0.56	0.521
426.530	0.8125	0.58	0.6667	0.39	0.479
484.864	0.9375	0.74	0.5833	0.32	0.521
580.533	1	0.83	0.0833	0	0.083

T2* mapping can be used to depict depth-dependent relaxation stratification in healthy cartilage, which may be lost in cartilage damage [3]. Although an in-plane resolution of 233 μm was achieved in the present study, an even higher resolution would be necessary to allow delineation of cartilage layer architecture in MCPs. This possible diagnostic virtue of T2* mapping could not be exploited in the present study, and further studies are needed to assess the diagnostic value of depth-dependent T2* relaxativity in RA.

Native T1 mapping has been proposed to be sensitive to cartilage degeneration in patients with knee OA with increased T1 values in OA [14]. However, compared to dGEMRIC, it has lower power to discriminate knee OA from healthy controls [14]. Our results corroborate the finding that native T1 mapping alone is of limited value in the assessment of cartilage quality.

dGEMRIC is an established quantitative imaging technique sensitive to cartilage degeneration [7, 8, 34, 38–40]. Our data support its sensitivity for cartilage degeneration in RA. In the present study, dGEMRIC was superior to T2* mapping and native T1 mapping in discriminating RA patients from healthy controls.

Low dGEMRIC values are considered to represent Gd $(DTPA)^{2-}$ accumulation within areas of GAG depletion [7]. However, the majority of publications using the dGEMRIC technique report on findings in patients with degenerative osteoarthritis [8]. In RA patients, highly active inflammatory changes can be seen with severely increased joint perfusion [24]. The effect of hyperperfusion and increased $Gd(DTPA)^{2-}$ concentration in joint inflammation on dGEMRIC values has not yet been systematically explored and awaits further evaluation. In chondromalacia and osteoarthritis of the patella, altered perfusion with MR-contrast agent has been demonstrated, possibly reflecting changes in intrachondral microvascularity and vascular permeability [41]. No reports on the microvascularity of the cartilage in RA are present in the literature, and further studies are needed to address this topic. However, factors other than GAG depletion alone need to be taken into account in the discussion of dGEMRIC in RA patients. In the absence of cartilage thinning, dGEMRIC abnormalities in RA may point towards cartilage damage on a molecular rather than on a macroscopic level.

The area under the curve (AUC) of ΔR1 in the discrimination of RA patients from healthy controls was lower than the AUC of dGEMRIC in the present study.

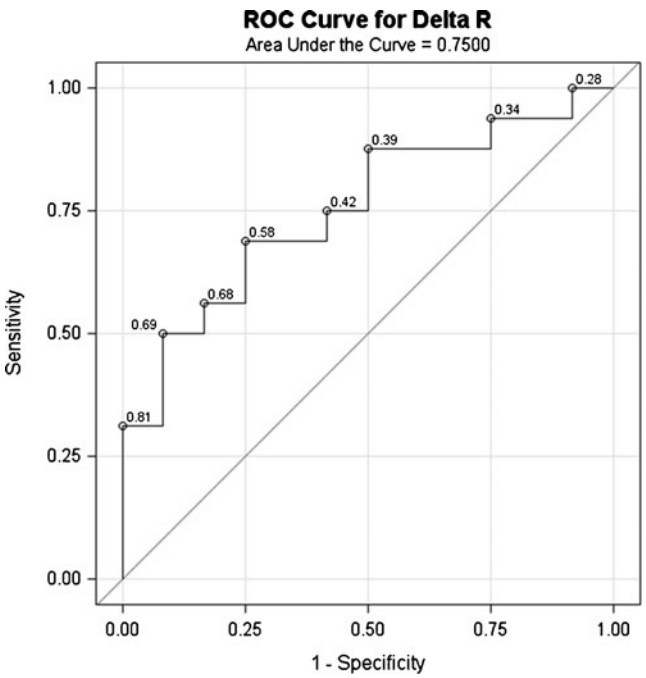

Fig. 5 Receiver operating characteristic (ROC) curve for ΔR1

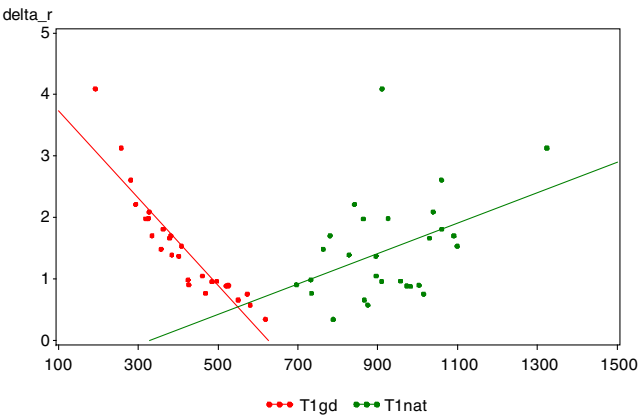

Fig. 6 Correlation of ΔR1 with $T1_{Gd}$ and native T1

Corroborating earlier findings [14, 15], there was a highly significant correlation between ΔR1 and $T1_{Gd}$ (dGEMRIC index). This correlation is inherent to the calculation of ΔR1 (Eq. 2): since $T1_{Gd}$ is lower than native T1 (due to the application of gadolinium), $1/T1_{Gd}$ is larger than 1/T1 and the effect of $T1_{Gd}$ on ΔR1 is higher than of native T1. These results indicate a close correlation between ΔR1 and $T1_{Gd}$ which is not linear but reflects the reciprocal character of Eq. 2. However, the high value of Pearson's correlation coefficient (r=−0.92) demonstrates that for native T1 and $T1_{Gd}$ values occurring in MCP joint cartilage of RA patients, the correlation between ΔR1 and $T1_{Gd}$ can be assumed to be almost linear.

In the evaluation of degenerative cartilage disorders of the knee, ΔR1 has been shown to be of slightly higher discriminative value than dGEMRIC [14]. In early OA of the hip, a linear correlation between ΔR1 and dGEMRIC has been demonstrated [15], and no additional value of ΔR1 has been assumed by the respective authors. In both studies the drawback of additional pre-contrast MRI has been discussed, and both groups conclude in accordance with our data that dGEMRIC is sufficient in the evaluation of cartilage damage.

Clinical signs of inflammation and CRP did not correlate significantly with T2*, native T1, dGEMRIC or ΔR1 values. However, the CIMESTRA study reports on a correlation between markers of cartilage catabolism (C-telopeptide of collagen II) and disease [42]. DAS 28 and CRP represent systemic inflammation beyond the single joint examined in MRI and are not specific; involvement of MCP II was an inclusion criterion in the present study and severe inflammation of other joints did not lead to exclusion. Perfusion-weighted MRI has been proposed as a tool to assess inflammatory activity [24] and may be useful to evaluate the influence of inflammation on cartilage quality in future MRI studies.

The present study has limitations. One is the limited number of subjects involved in this study. This is reflected by broad confidence intervals for sensitivity and specificity, for example. Non-invasive measures of cartilage quality were assessed and no cartilage biopsy, histology or biochemistry was available. As in the majority of in vivo studies on cartilage quality, a true gold standard reflecting the condition of the cartilage is lacking. Specificity and sensitivity values have been calculated under the assumption that cartilage degeneration was present in all RA patients. However, due to the lack of a gold standard, the true incidence of cartilage damage in our group remains unknown. Using the above stated cut off values, a number of patients could possibly be assumed to have normal cartilage. Further studies are needed to assess sensitivity and specificity of non-invasive evaluation of cartilage quality in RA using a true gold standard such as histology or arthroscopy. T2* stratification as one possible diagnostic feature of T2* mapping could not be exploited in the present study, and further studies are needed to assess the diagnostic value of T2* relaxativity stratification in RA. dGEMRIC used a 40 min delay after Gd administration. Since the positioning in the MR scanner can be uncomfortable or even painful for arthritis patients, the patients were allowed to stand up and move during the waiting period. This way, native T1 and dGEMRIC images were not coregistered the way they can be in in vitro studies, and no ΔR1 maps could be calculated.

In conclusion, our results support the use of post-contrast dGEMRIC for the assessment of MCP joint cartilage quality in RA. In our study, T2* and native T1 mapping were of low diagnostic value, compared to dGEMRIC. Pre-contrast T1 mapping for the calculation of ΔR1 is time consuming, inconvenient for the patient and did not increase the diagnostic value of dGEMRIC in our study population. Further study is needed to compare the different techniques of biochemical cartilage MRI in RA.

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