Delayed gadolinium enhanced MRI of menisci and cartilage (dGEMRIM/dGEMRIC) in obese patients with knee osteoarthritis: Cross sectional study of 85 obese patients with intra-articular administered gadolinium contrast.

ABSTRACT

Background: Early cartilage changes in knee osteoarthritis (OA) can be assessed by both intravenous (i.v.) and intra-articular (i.a.) delayed Gadolinium enhanced MRI of cartilage (dGEMRIC).

Purpose: To examine the relationship between i.a. dGEMRIC and delayed Gadolinium enhanced MRI of menisci (dGEMRIM), and to investigate if the approach can be used to assess the morphological degeneration of menisci in obese patients with knee OA.

Study Type: Cross-sectional

Population: 85 obese patients with knee OA

Field strength/sequences: 1.5T. Inversion recovery sequence with four inversion times.

Assessment: T1-relaxation times were calculated for posterior weight bearing femoral cartilage and the posterior horns of the menisci. Meniscus degeneration sum score (0-2) was assessed as increased signal/no signal (1/0) and tear/no tear (1/0).

Statistical Tests: T1-relaxation times were compared using Student's t-test. Comparison of cartilage and meniscus T1-relaxation times was done by regression analysis. ANOVA was used for comparison of meniscal T1-relaxation times among the three summed morphological scores (0-2). Statistical analyses were performed with a level of significance at 0.05.

Results: For lateral menisci, morphology sum scores of 0, 1 and 2 were found in 13, 58 and 14 patients and for medial menisci in 2, 30 and 30 patients, respectively. Mean T1-relaxation time were 441 ms, 480 ms and 497 ms for cartilage, lateral menisci, and medial menisci. T1-relaxation times for the menisci were similar ($p=0.53$), and a weak correlation was found between dGEMRIC and dGEMRIM in the lateral compartments ($R= 0.26$). Comparing dGEMRIM between different morphology sum scores showed no differences ($p>0.4$).

Conclusion: I.a. dGEMRIM showed no correlation between the degree of meniscal degeneration and meniscus T1-relaxation times. I.a. dGEMRIM do not seem to deliver useful information about meniscus degeneration to be suitable for clinical applications, but i.a. dGEMRIC may still be considered an alternative contrast saving method for cartilage.

Keywords: Gadolinium, Osteoarthritis, Contrast enhanced MRI, Meniscus, Cartilage

INTRODUCTION

Symptomatic knee osteoarthritis (OA) is highly prevalent and affects nearly 10% among people above the age of 50 and leads to frequent disability (1). The pathogenesis for knee OA is still unanswered, but obesity is one of main risk factors. Knee OA is considered a whole-joint disease involving all tissue components, i.e. ligaments, cartilage, periarticular muscles, menisci and subchondral bone (2). The menisci play an important role in shock absorbing and load distribution. Loss of meniscal function and morphologic changes in the menisci are highly associated with developing knee OA (3;4) and predictive of future joint replacement (5;6) In knee OA, cartilage degeneration is related to loss of collagen and glycosaminoglycans (GAG)(1;7). Delayed gadolinium enhanced MRI of Cartilage (dGEMRIC) is a well-known method to study early cartilage changes related to GAG-depletion (8-10). dGEMRIC is usually performed using a negatively charged Gadolinium (Gd-$DTPA^{2-}$, Magnevist®) contrast injected intravenously (i.v.) in a double dose (0.2 mmol/kg) with subsequent delayed MRI scanning after 90-120 minutes with either two-dimensional inversion recovery, three-dimensional Look-Locker, or three-dimensional variable flip angle (11) . With this method, the passive diffusion of negatively charged Gadolinium (Gd) into cartilage has shown an inverse linear correlation to the amount of GAGs in the articular knee cartilage (9;12) . Since menisci and cartilage share a collagen matrix and GAG molecules, the same method has been used to study the menisci, called delayed gadolinium enhanced MRI of menisci (dGEMRIM) (13-16). Even though the amount of GAG is around 1% in the menisci and 5-10 % in cartilage (17;18) **,** a study by Sigurdsson et al. have shown that menisci and cartilage can be examined simultaneously by i.v. dGEMRIC using Gd-$DTPA^{2-}$ preferably 90 minute after contrast (15). The i.v. dGEMRIM approach has today only been used in a few studies using predominantly healthy participants(13-16) and even though the results are not directly comparable according to the magnetic field strength and MRI methods (3D look locker vs. inversion recovery) , there seems

to be some discrepancy, especially concerning the question of whether the concentration of GAGs increases or decreases in the menisci during morphological degeneration.

With the recent regulatory warning from both US Food and Drug Administration (FDA) and European Medicines Agency EMA (19) about the use of i.v. Gd-contrast, other methods to reduce the amount of Gd are warranted. A few groups have used ultrasound guided intra articular (i.a.) injection of contrast to perform dGEMRIC and have shown that other negatively charged Gd compounds like Gd-BOPTA (Multihance®) can be used for i.a. dGEMRIC (30) in the hip and knee(20-22), resulting in excellent cartilage delineation and contrast penetration in GAG depleted cartilage using less than 1/1000 contrast dose compared to the i.v. dGEMRIC approach(22).

Thus the aim of this study was to assess the association between i.a. dGEMRIC and dGEMRIM using i.a. Gd-BOPTA and to assess if i.a. dGEMRIM could separate various degrees of meniscal degeneration. We hypothesized that i.a. dGEMRIM would correlate to both i.a. dGEMRIC and the meniscus degeneration similar to what have been seen with the i.v. method.

MATERIALS AND METHODS

Patients

Eighty-five obese patients from the CAROT-study (Clin trial id: NCT00655941) were included. Patients were recruited between November 2007 and August 2008 at the outpatient clinic at the Department of Rheumatology, Frederiksberg Hospital, Denmark. The study was approved by the ethical committee and medical drug agency (H-B-2007-088). The inclusion criteria were as follows: Age> 50, BMI≥ 30 kg/m^2, and primary symptomatic (pain) knee OA, diagnosed according to the American College of Rheumatology (ACR), verified by radiographic criteria, with KLG≥2 (19). Patients with KLG-4 were included, as these patients often have preserved cartilage in the lateral tibiofemoral-compartment. In these cases cartilage and thus dGEMRIC data from the compartment determining the KLG-4 grade was not included in the analysis due to missing cartilage.

One Hundred Ninety Two patients were included in the CAROT-study, but due to movement of the leg between the four inversion times of the dGEMRIC/dGEMRIM method (see below) and subsequent difficulties in motion correction between temporal slices we ended up with 85 suitable datasets, corresponding to 85 patients with 85 knees, for dGEMRIC/dGEMRIM analysis. Suitability was decided visually and subjectively after application of "motion correction" using an in-house MATLAB based software (Mokkula, Mathworks R2014, Natick, MA). The software will depict and correct rigid translation between the different timeframes whereas any movement that is not rigid translation (i.e. knee rotation, or rigid translation but not in-plane) will show significant residual motion artifacts in the images that affect the maps resulting in higher and more heterogeneous T1 (Gd) values, which were excluded from the analysis. All data in this study are baseline data and baseline MRIs before initiation of weight loss intervention.

Radiographs

Standardised posterior-anterior standing radiographs of the target knee joints were obtained in a semi-flexed position of approximately 30 degrees and scored according to the Kellgren and Lawrence grading (KLG) system (23) by a skilled musculoskeletal (MSK)-radiologist (MB, 20 years of MSK experience).

Ultrasound and MRI

Prior to MRIs, an ultrasound examination was performed. The target joint was aspirated for excessive joint fluid, followed by an ultrasound-guided i.a. injection of 0.1 ml Gd-BOPTA (0.5 mmol/ml) added to 10 ml Lidocaine 1%, given a concentration of approximately 4mmol/l.

Following the injection, the patients walked for 15-20 minutes on stairs, and 90-120 minutes after injection MRI of the target knee was performed on a Philips Intera 1.5 Tesla MRI scanner (Philips Medical Systems, Eindhoven, The Netherlands; software release 12.1.5.0). Patients were lying in the supine position, using a flex sense coil and the following MRI-protocol: Three plane GRE localizer, Coronal T1-weighted SE, Sagittal 2D PD-weighted fat-saturated (reference scan when fusing dGEMRIC scans) and four sagittal inversion recovery T1-weighted measurements (TI = 50, 350, 650, 1410 ms) for dGEMRIC. DGEMRIC was done in 2 sagittal- slices of the medial and lateral tibiofemoral compartment of the knee. Each inversion time took 7 minutes scan time due to the scanner configuration and the use of a large flex coil (obese knees). The technologists performing the examinations were trained to position the most lateral and medial sagittal slice in each compartment one centimeter inside the joint defined from a line connecting the outer bony margin of tibia and femur in the mid-coronal plane of the T1w images. It was from these two images that we choose the slice with best visible cartilage in each tibiofemoral compartment. Total scan time was 30 min.

For further MRI-details: please see supplementary files.

Image analysis

dGEMRIM/dGEMRIC

The lateral, sagittal slide with best preserved cartilage and posterior meniscus was chosen for analysis of dGEMRIC/dGEMRIM. The medial sagittal slide with best preserved posterior meniscus was chosen for analysis. Due to advanced knee OA, cartilage in the weight bearing part of the medial compartment was not representative on both femur and tibia in most cases. Region of interest (ROI) for dGEMRIC was the posterior weight-bearing femoral knee cartilage delimited of the posterior menisci on sagittal MRI scans as described by Tiderius et al.(24) . The meniscal ROIs were the entire posterior horn visualised on the same sagittal slide as the dGEMRIC ROI (Fig. 1).

Fig 1

T1-relaxation times were calculated using an in-house MATLAB based software (Mokkula, Mathworks R2014, Natick, MA). The reported T1-relaxation times are the averages of the T1-relaxation times in the given ROIs.

Intra- and inter-observer reliabilities for the T1 quantification were based on analysis of 20 randomly selected scans evaluated twice by SH and by CD with one month interval. Inter observer analysis between SH and CD was done using the same 20 scans.

Meniscus Morphology

The same two slices used for dGEMRIM/dGEMRIC-analysis (one lateral and one medial) were used for characterisation of meniscal degeneration using the sagittal fat-saturated PD-weighed sequence. The menisci were scored by MB with 20 years of experience in MSK radiology as

"Increased signal" and/or "Tear lesion" using a dichotomized score of Yes /No, (Yes=1 and No= 0), using the definitions proposed by the MRI osteoarthritis knee score (MOAKS)(25), . The two scores were summed resulting in three sum score groups (0, 1 and 2) as a surrogate measure of meniscal degeneration (Fig. 2).

Statistics

T1-relaxation times for lateral and medial menisci were compared using paired t-testing. Comparison of cartilage and meniscus T1-relaxation times was done by regression analysis. One way ANOVA was used for comparison of meniscal T1-relaxation times among the three summed morphological group scores. All statistical analyses were performed in SAS 9.4 with a two-sided level of significance at 0.05.

RESULTS

Characterization of participants

The mean age of the 85 participants (63 women) was 62 years (range 51-78). Mean BMI was 37 (range 30-51) kg/m^2. The median KLG was 3 (range 2-4).

Reproducibility analysis

ICCs were 0.90 and 0.88 for intra-reader and inter-reader reliability

Analysis of dGEMRIC/dGEMRIM and Meniscus Morphology

For dGEMRIC of the posterior femoral cartilage (N=85) the mean T1-relaxation time was 441 ms (range 300-571 ms). DGEMRIM of the lateral meniscus (N=85) showed mean T1-relaxation time of 497 ms (range 291-693 ms) and dGEMRIM for the medial menisci (N=62) mean T1-relaxation

time was 480 ms (range 263-699). For lateral meniscus, 13 patients had normal signal and no tear lesions, 72 patients had increased signal and out of these 14 had concomitant Tear lesions; resulting in 13 patients with meniscus morphology score 0, 58 with score 1, and 14 with score 2. For the medial meniscus, only 2 patients had no morphology or tear changes (score 0), 30 patients had increased signal and no tear lesions (score 1) and 30 patients had both increased signal and tear lesions (score 2). Table 1 shows mean T1-relaxation times and range for each of the three morphological groups.

Table 1

In addition, an analysis excluding the meniscal tear group was done to compare lateral dGEMRIM in patients with no tear (N=13) and a morphology sum of 1 (N=58) using student's t-test which did not show any difference between the groups (p=0.1).

Correlations of dGEMRIC/dGEMRIM

Comparing dGEMRIC and dGEMRIM in the lateral compartment revealed a low , but significant correlation (R= 0.26 and p=0.02).

Fig 3

Comparing the lateral and medial menisci dGEMRIM T1-relaxation times using paired t-test showed no difference (p=0.53), also illustrated by a correlation analysis showing an R of 0.62 ($p<0.0001$).

Fig. 4

Comparison of dGEMRIM and Morphology score

One way ANOVA was used for comparison of dGEMRIM T1-relaxation times between the three degrees of morphological menisci degeneration.

Fig. 5

We found no differences in T1 relaxation times between the three groups, for neither medial (p= 0.41) nor lateral (p=0.97) menisci,. In order to eliminate the T1 influence of fluid in torn menisci, we compared dGEMRIM levels in menisci with normal signal no tear (N=13) to increased signal no tear meniscal (N=58) using a student's t-test, revealing no difference (p= 0.10).

DISCUSSION

In this study we used i.a. Gd-BOPTA instead of the conventional double dose (0.2 mmol/kg) i.v. Gd-DTPA^{2-} for dGEMRIC/dGEMRIM, which is known to reduce the contrast dose to less than 1/1000 (20-22) . The overall aim of this study was to study the association between i.a. dGEMRIC-dGEMRIM using Gd-BOPTA and the relation between i.a. dGEMRIM and meniscal degeneration

We found a weak but statistically significant correlation between i.a. dGEMRIC and dGEMRIM T1-relaxation times in the lateral tibiofemoral compartment supporting a concomitant degeneration in the two tissues that is not explained by the morphological scores or by the KL grade. It may be that dGEMRIM is sensitive to biochemical changes within intact menisci that are not appreciable by a binary grading of signal intensity within meniscus on morphologic MRI or by the radiological KLG scores. This finding supports the assumption of knee OA as a whole joint disease (26), but the result should be interpreted with care as the statistically significance mainly might be caused by the number of patients. Nevertheless our findings are in concordance with a study using i.v. dGEMRIC/dGEMRIM and Gd-DTPA^{2-} by Van Tiel et al. showing a trend towards lower T1-relaxation time in degenerated menisci compared to normal menisci, and a positive correlation between dGEMRIM and dGEMRIC, in both the lateral (moderate correlation) and medial (strong correlation) compartments (16). Krishnan et al. also found a correlation between articular dGEMRIC and dGEMRIM in healthy volunteers and patients without OA but with knee complaints (14).

The second objective was to study the relationship between i.a. dGEMRIM and meniscus degeneration in obese patients with knee OA. We hypothesized that the meniscal T1-relaxation times would decrease in the same manner as for cartilage with increasing severity of morphological change in menisci. For this analysis we compared well defined meniscal morphology scores from

the MOAKS publication(25) and T1-relaxation times for each knee compartment separately. Neither the medial nor lateral compartment showed any correlation between the two parameters, indicating that i.a. dGEMRIM doesn´t change with the applied meniscal degeneration scores. Thus the i.a. dGEMRIM method cannot be recommended to study meniscal degeneration in obese OA patients.

This finding is in accordance with previous findings using the i.v. dGEMRIM method, comparing various degrees of meniscal degeneration with both dGEMRIM (15) and content of proteoglycans from biopsies (27). Other groups using the i.v. dGEMRIM approach like Sigurdsson et al(15) found a reverse U-shaped dGEMRIM patterns at different stages of meniscus lesions with increasing dGEMRIM for the moderate meniscal degenerations degrees that decreased for high grades, (15) ,and in a histologic study by Sun Y et al they found that severe loss of collagen and increasing concentration of proteoglycans were hallmarks of OA degenerated menisci (27), which is the reverse process of GAG behavior in cartilage. Finally Krishnan et al. found no correlation between i.v. dGEMRIM and meniscus degeneration when degeneration was scored according to the 0-4 scale by Hunter et al (14;28).

An explanation for our finding could be that the GAG content in menisci is only 1/10 the GAG content of articular cartilage and that the collagen network differs between the two tissue types(27). Another major confounder of why i.a. dGEMRIM and dGEMRIC differs from the i.v. method may be found in the anatomy of the meniscus that is divided into the small peripheral region called the red zone (Zone 1) holding the blood supply, an intermediate area (Zone 2) and completely avascular inner zone known as the white zone (Zone 3)(29) . Using i.a. dGEMRIC will therefore exclude the red zone to contribute to the dGEMRIM values that will only be generated from the passive diffusion of contrast into primarily Zone 3.

Gd-BOPTA was chosen as it potentially is better than Gd-$DTPA^{2-}$ for dGEMRIC due to the higher relaxability, which in theory could better separate normal cartilage from early GAG-depleted cartilage. In addition an animal study had shown that i.a. Gd-BOPTA could be used for dGEMRIC at the time of study, and finally (30) for economic reasons it was an advantageous to use Gd-BOPTA at our site..

It can be discussed whether i.a. contrast administration for dGEMRIC and dGEMRIM is a limitation or strength. Strengths are; that the contrast dose is much lower, the dose is not influenced by the body mass index (BMI) and i.a. Gd has been shown to provide similar or better cartilage delineation (20;31) . A limitation is that the T1-relaxation times after i.a. contrast application seem to only provide passive diffusion of Gd into primarily Zone 3 of the menisci for dGEMRIM and that dGEMRIC values are significantly lower in the cartilage when comparing to the values seen after i.v. Gd contrast administration(18) making direct comparison between the i.a. and i.v. method challenging. However, we believe that this point is relative irrelevant in studies dealing with relative T1-changes over time.

Another limitation of the this study was the acquisition time where every four inversion recovery took 7 min resulting in only two sagittal slices per compartment from which we the one with the best preserved cartilage and meniscus was chosen. In future studies using modern scanners and higher field strength like 3T allows for whole joint 3D dGEMRIC and dGEMRIM within a reasonable scan time. These scanners also provide the possibility to add other compositional MRI-methods, like T2- and T1rho maps that has shown to add additional value for mapping collagen orientation (T2-maps) and GAG content (T1-rho) without the use of Gd-contrast (32) A final limitation in this study was that we only examined cartilage from lateral femoral condyle for dGEMRIC. This was due to the severity of knee OA in the medial compartment displayed by a

median KL grade of 3. In addition we were challenged by significant movement between the temporal slices of the dGEMRIC/dGEMRIC sequence preventing proper motion correction which resulted in fewer patients than included in the entire CAROT-study.

In conclusion, we found no correlation between the degree of meniscal degeneration and meniscus T1-relaxation times. Even though the i.a. dGEMRIM method cannot be directly compared to i.v, the findings suggest that i.a. dGEMRIM does not seem to deliver useful information about meniscus degeneration and is therefore not suitable for clinical or research applications. However we do see an association between dGEMRIC and dGEMRIM supporting a concomitant degeneration in the two tissues that is not explained by the morphological scores or by the KL grade. Thus i.a. dGEMRIC may still be an alternative contrast saving methods to consider taking the recent regulatory warnings regarding the use of i.v. Gadolinium in mind.

Figure legends

Figure 1. Sagittal view of lateral knee compartment with dGEMRIC* and dGEMRIM** ROIs.

Figure 2. Meniscus Morphology score. A) normal signal, no tear. B) Increased Signal, No Tear. C) and D) Increased signal and Tear lesion.

Figure 3. Correlation between T1-relaxation times (ms) in lateral posterior femoral cartilage (Lat femoral cartilage) and lateral meniscus (Lat meniscus). R= 0.26 (p=0.02).

Figure 4. Correlation between T1-relaxation times (ms) in medial meniscus (Med meniscus) and lateral meniscus (Lat meniscus). R=0.62 ($p<0.0001$).

Figure 5. Comparison of T1-relaxation times from the menisci to the meniscus morphology score. Separated in medial and lateral compartment.

Table 1. Patient characteristics, Meniscus morphology score and T1- relaxation times (ms) for menisci and articular cartilage.

Reference List

(1) Busija L, Bridgett L, Williams SR, et al. Osteoarthritis. Best Pract Res Clin Rheumatol 2010 December;24(6):757-68.

(2) Poole AR. Osteoarthritis as a whole joint disease. HSS J 2012 February;8(1):4-6.

(3) Englund M, Haugen IK, Guermazi A, et al. Evidence that Meniscus Damage May Be a Component of Osteoarthritis: the Framingham Study. Osteoarthritis Cartilage 2016 February 28;24(2):270-3.

(4) Berthiaume M, Raynauld J, Martel-Pelletier J, et al. Meniscal tear and extrusion are strongly associated with progression of symptomatic knee osteoarthritis as assessed by quantitative magnetic resonance imaging. Ann Rheum Dis 2005 April 16;64(4):556-63.

(5) Roemer FW, Kwoh CK, Hannon MJ, et al. Can Structural Joint Damage Measured with MR Imaging Be Used to Predict Knee Replacement in the Following Year? Radiology 2014 October 3;274(3):810-20.

(6) Roemer FW, Kwoh CK, Hunter DJ, et al. Knees with medial mensical pathology are more likely to undergo total knee replacement: a cross-sectional analysis from the osteoarthritis initiative. Osteoarthritis and Cartilage 2012;20(Supplement 1):S220.

(7) Poole AR, Rizkalla G, Ionescu M, et al. Osteoarthritis in the human knee: a dynamic process of cartilage matrix degradation, synthesis and reorganization. Agents Actions Suppl 1993;39:3-13.

(8) Bashir A, Gray ML, Burstein D. Gd-DTPA2- as a measure of cartilage degradation. Magn Reson Med 1996;36(5):665-73.

(9) Bashir A, Gray ML, Boutin RD, Burstein D. Glycosaminoglycan in articular cartilage: in vivo assessment with delayed Gd(DTPA)(2-)-enhanced MR imaging. Radiology 1997 November 1;205(2):551-8.

(10) Crema MD, Roemer FW, Marra MD, et al. Articular cartilage in the knee: current MR imaging techniques and applications in clinical practice and research. Radiographics 2011 January;31(1):37-61.

(11) Siversson C, Tiderius CJ, Neuman P, Dahlberg L, Svensson J. Repeatability of T1-quantification in dGEMRIC for three different acquisition techniques: two-dimensional inversion recovery, three-dimensional look locker, and three-dimensional variable flip angle. J Magn Reson Imaging 2010 May;31(5):1203-9.

(12) Bashir A, Gray ML, Hartke J, Burstein D. Nondestructive imaging of human cartilage glycosaminoglycan concentration by MRI. Magn Reson Med 1999 May;41(5):857-65.

(13) Sigurdsson U, Siversson C, Lammentausta E, Svensson J, Tiderius CJ, Dahlberg L. In vivo transport of Gd-DTPA2- into human meniscus and cartilage assessed with delayed gadolinium-enhanced MRI of cartilage (dGEMRIC). BMC Musculoskeletal Disorders 2014;15(1):226.

(14) Krishnan N, Shetty SK, Williams A, Mikulis B, McKenzie C, Burstein D. Delayed gadolinium-enhanced magnetic resonance imaging of the meniscus: An index of meniscal tissue degeneration? Arthritis & Rheumatism 2007 May 1;56(5):1507-11.

(15) Sigurdsson U, Møller G, Siversson C, et al. Delayed gadolinium-enhanced MRI of meniscus (dGEMRIM) and cartilage (dGEMRIC) in healthy knees and in knees with different stages of meniscus pathology. BMC Musculoskeletal Disorders 2016 September 29;17:406.

(16) van TJ, Kotek G, Reijman M, et al. Delayed gadolinium-enhanced MRI of the meniscus (dGEMRIM) in patients with knee osteoarthritis: relation with meniscal degeneration on conventional MRI, reproducibility, and correlation with dGEMRIC. Eur Radiol 2014 May 10.

(17) Herwig J, Egner E, Buddecke E. Chemical changes of human knee joint menisci in various stages of degeneration. Ann Rheum Dis 1984;43(4):635-40.

(18) McNicol D, Roughley PJ. Extraction and characterization of proteoglycan from human meniscus. Biochem J 1980;185(3):705-13.

(19) European Medicines Agency. EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans. 625317. 23-11-2017.

Ref Type: Online Source

(20) Boesen M, Jensen KE, Qvistgaard E, et al. Delayed gadolinium-enhanced magnetic resonance imaging (dGEMRIC) of hip joint cartilage: better cartilage

delineation after intra-articular than intravenous gadolinium injection. Acta Radiol 2006 May;47(4):391-6.

(21) Zilkens C, Miese F, Kim YJ, et al. Direct comparison of intra-articular versus intravenous delayed gadolinium-enhanced MRI of hip joint cartilage. J Magn Reson Imaging 2014 January 1;39(1):94-102.

(22) Hangaard S, Gudbergsen H, Skougaard M, et al. Point of no return for improvement of cartilage quality indicated by dGEMRIC before and after weight loss in patients with knee osteoarthritis: a cohort study. Acta Radiol 2018 March;59(3):336-40.

(23) KELLGREN JH, LAWRENCE JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957 December;16(4):494-502.

(24) Tiderius CJ, Tjörnstrand J, Aakeson P, Södersten K, Dahlberg L, Leander P. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC): Intra- and interobserver variability in standardized drawing of regions of interest. Acta Radiologica 2004 October 1;45(6):628-34.

(25) Hunter DJ, Guermazi A, Lo GH, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis and Cartilage 2011 August;19(8):990-1002.

(26) Hunter DJ, Arden N, Conaghan PG, et al , on behalf of the OARSI OA Imaging Working Group. Definition of osteoarthritis on MRI: results of a Delphi exercise. Osteoarthritis Cartilage 2011 August 12;19(8):963-9.

(27) Sun Y, Mauerhan DR, Kneisl JS, et al. Histological Examination of Collagen and Proteoglycan Changes in Osteoarthritic Menisci. Open Rheumatol J 2012 April 19;6:24-32.

(28) Hunter DJ, Zhang YQ, Niu JB, et al. The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis. Arthritis & Rheumatism 2006 March 1;54(3):795-801.

(29) Bryceland JK, Powell AJ, Nunn T. Knee Menisci: Structure, Function, and Management of Pathology. Cartilage 2017 April 22;8(2):99-104.

(30) Kwack KS, Cho JH, Kim MM, et al. Comparison study of intraarticular and intravenous gadolinium-enhanced magnetic resonance imaging of cartilage in a canine model. Acta Radiol 2008 February;49(1):65-74.

(31) Bittersohl B, Hosalkar HS, Werlen S, Trattnig S, Siebenrock KA, Mamisch TC. Intravenous versus intra-articular delayed gadolinium-enhanced magnetic resonance imaging in the hip joint: a comparative analysis. Invest Radiol 2010 September;45(9):538-42.

(32) Oei EHG, van Tiel J, Robinson WH, Gold GE. Quantitative radiological imaging techniques for articular cartilage composition: Towards early diagnosis and development of disease-modifying therapeutics for osteoarthritis. Arthritis Care Res (Hoboken) 2014 July 28;66(8):1129-41

Figure 1. Sagittal view of lateral knee compartment with dGEMRIC and dGEMRIM ROIs.

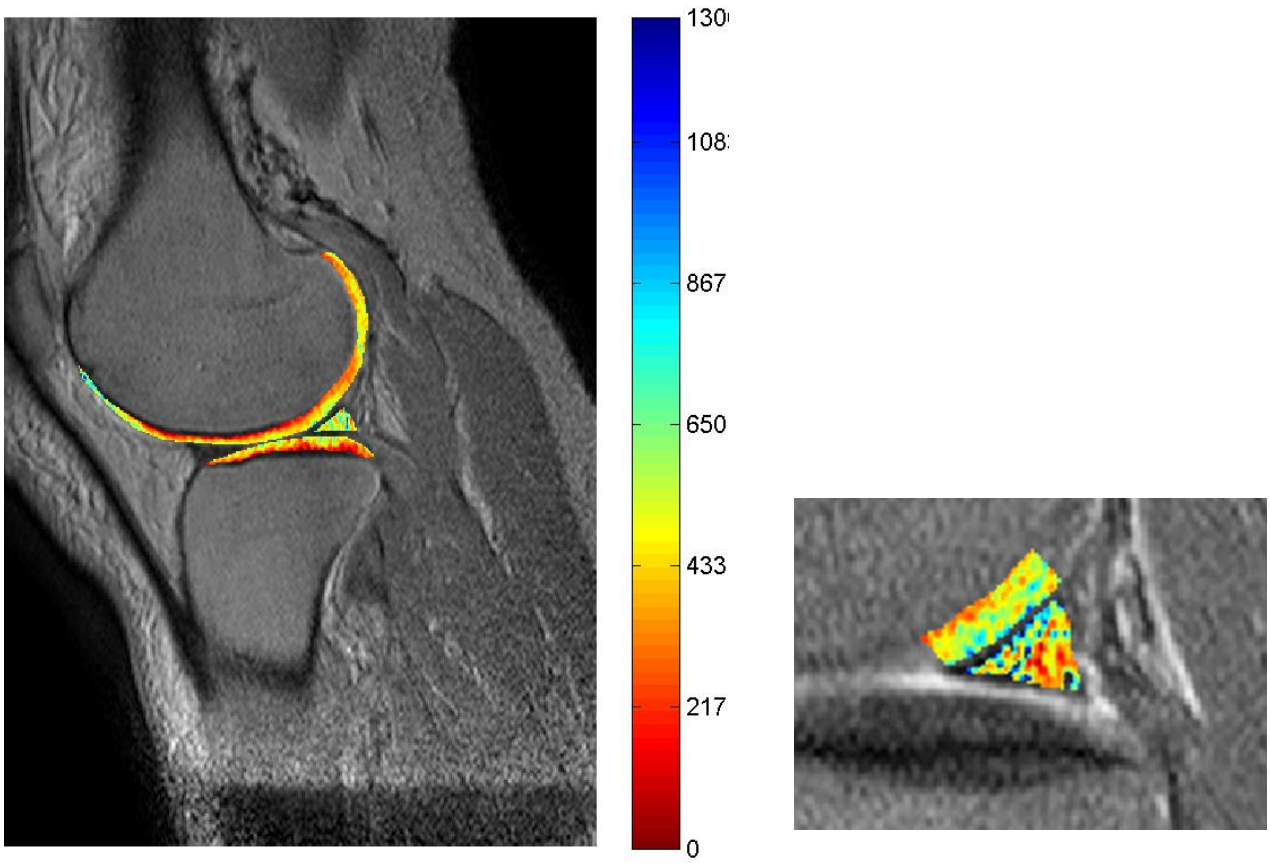
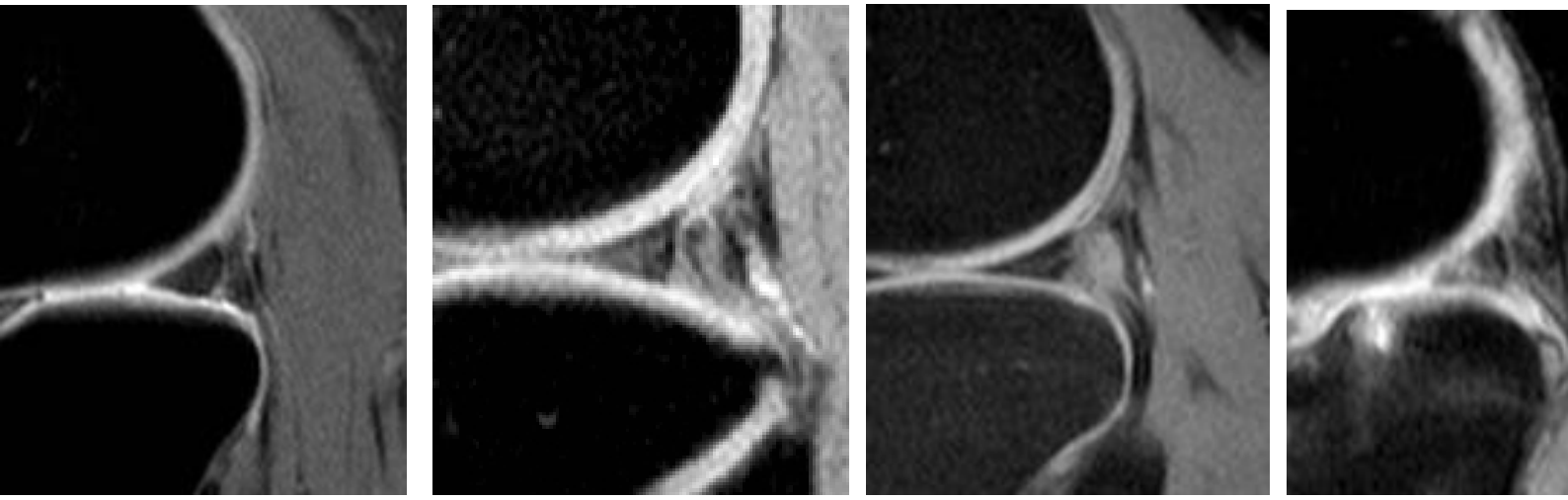


Fig. 2. Meniscus Morphology score. A) normal signal, no tear. B) Increased Signal, No Tear. C) and D) Increased signal and Tear lesion.



A
Signal 0
Tear 0

B
Signal 1
Tear 0

C
Signal 1
Tear 1

D
Signal 1
Tear 1

Figure 3. X-axis: Lateral posterior femoral cartilage T1-relaxation time (ms), Y-axis: Lateral meniscus T1-relaxation time (ms). R= 0.26 (p=0.02).

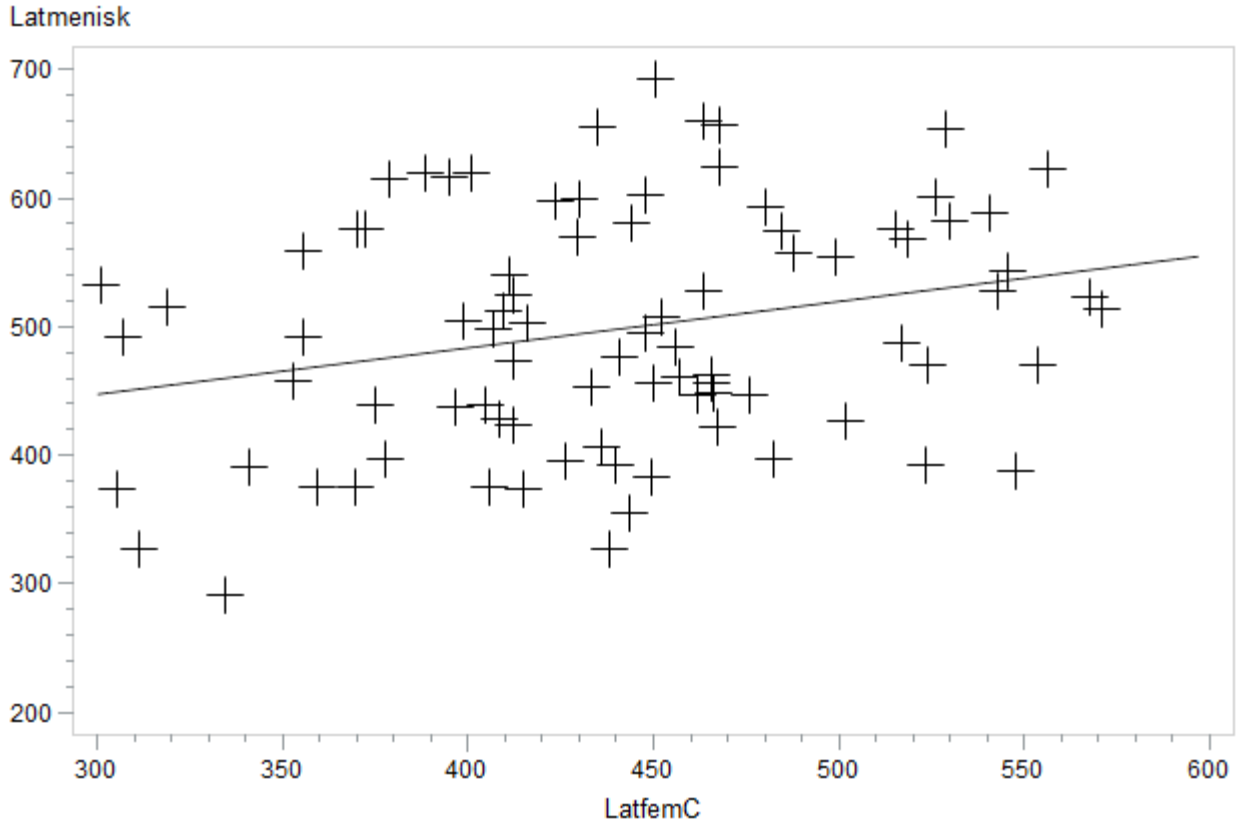


Figure 4. X-axis: Medial meniscus T1- relaxation time (ms), Y-axis: Lateral meniscus T1-relaxation rime (ms). R=0.62 ($p<0.0001$)

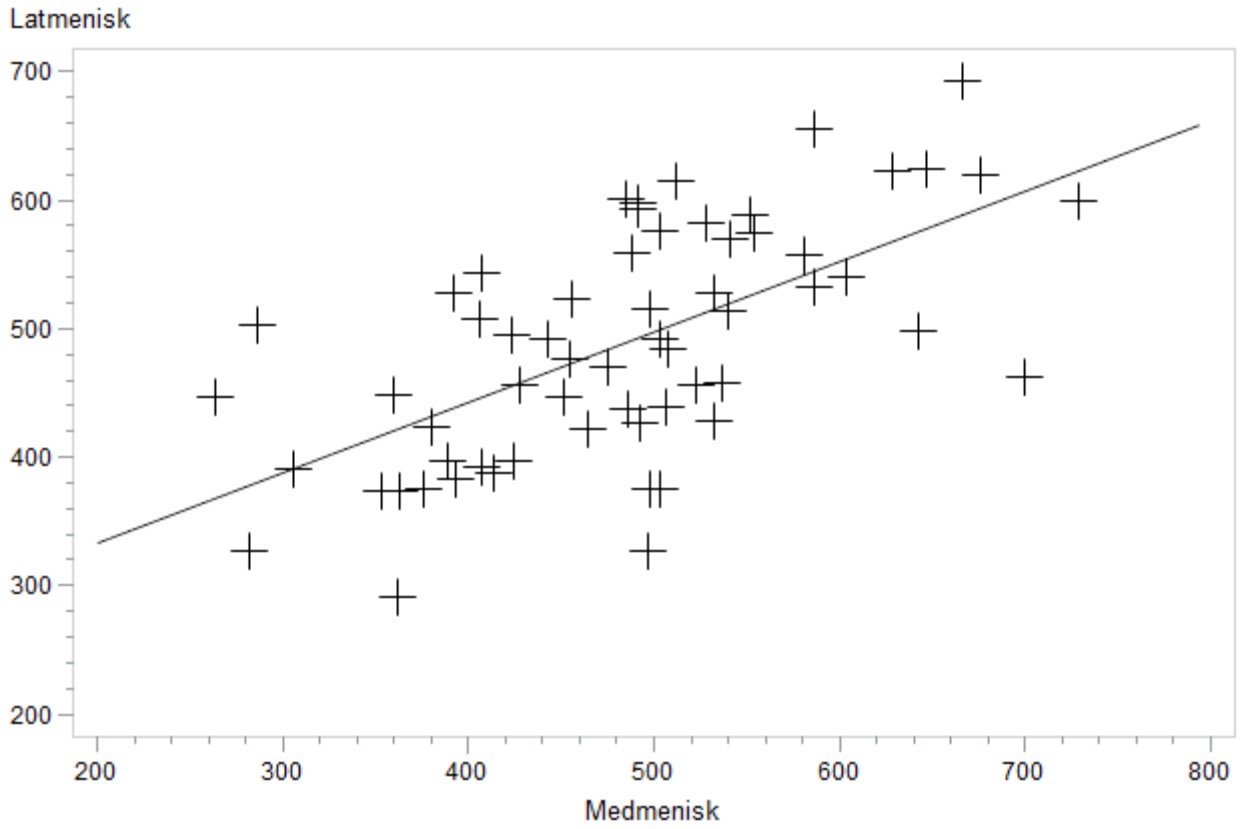
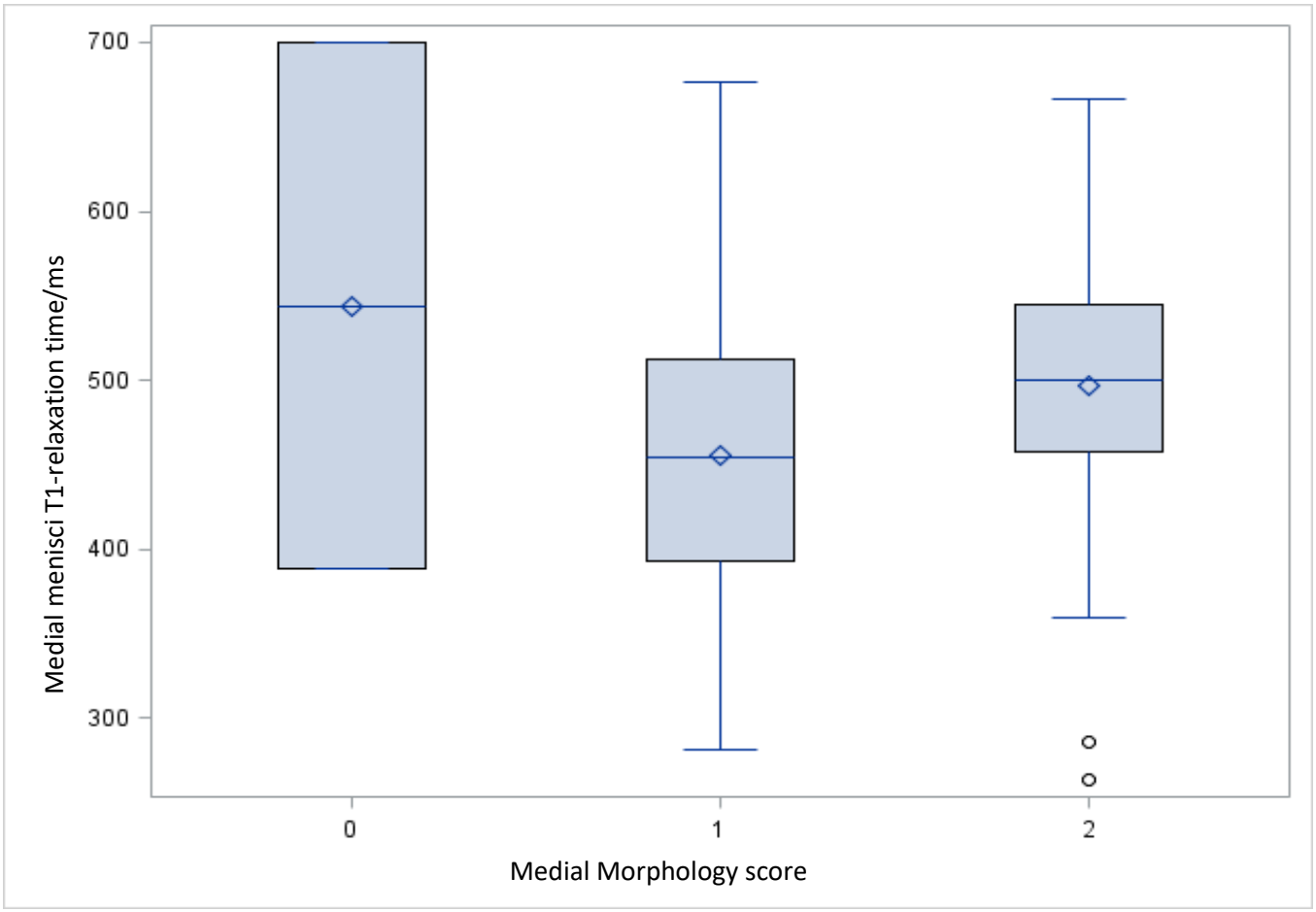


Fig. 5. Comparison of T1-relaxation times from the menisci to the meniscus morphology score. Separated in medial and lateral compartment.



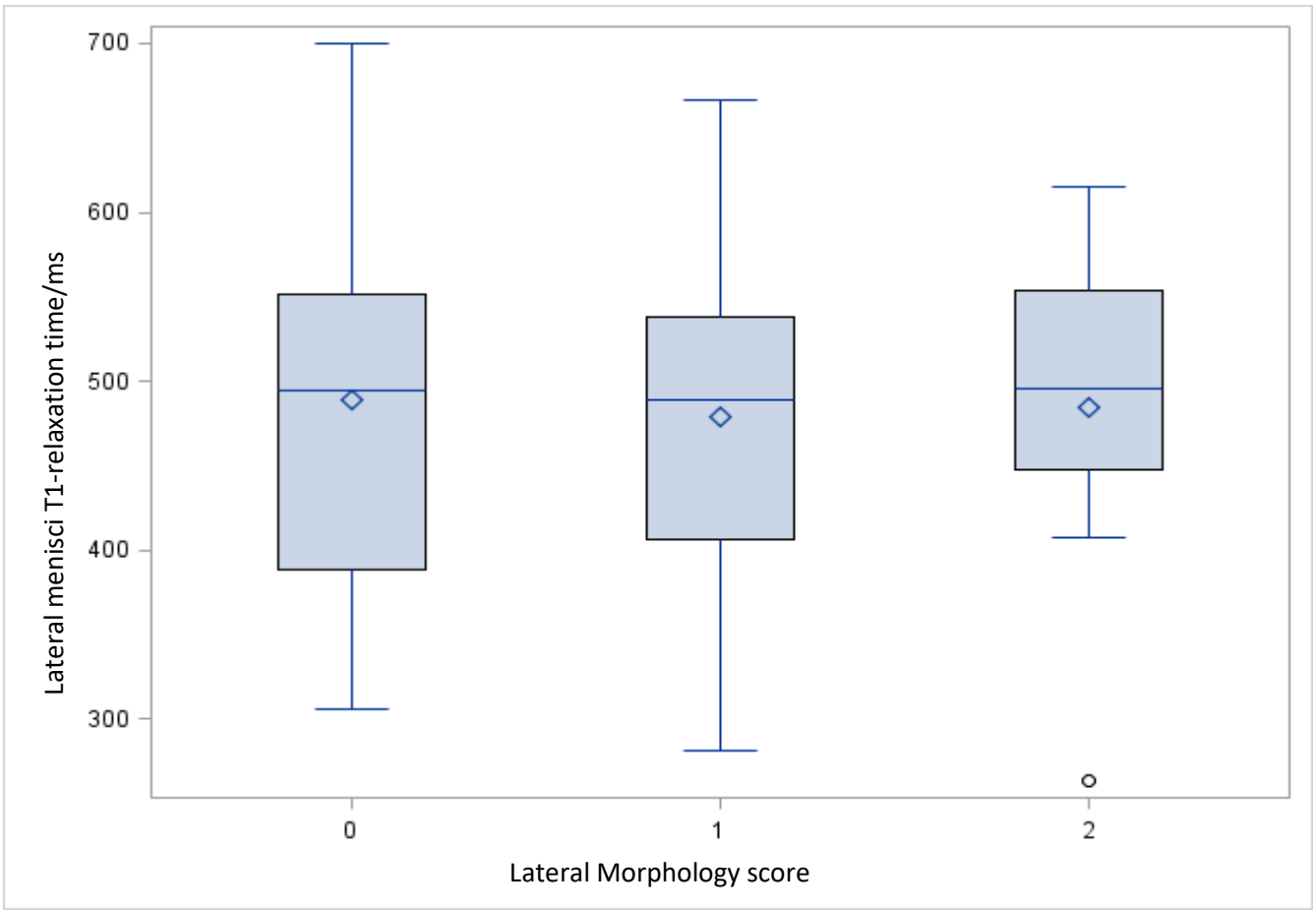


Table 1.Patient characteristics, Meniscus morphology score and T1- relaxation times for menisci and articular cartilage

	dGEMRIC	**dGEMRIM** **lat meniscus**	**dGEMRIM** **med meniscus**
Patients (N) BMI: mean 37 (30-51) KLG: median 3	85	84	62
T1 relaxation times/ms, range	441 (300;571)	497 (291;693)	480 (263;699)
Signal (Y/N)		72Y, 13N	60Y, 2N
Tear (Y/N)		14Y, 71N	30Y, 32N