Delayed Gadolinium-Enhanced MRI of Cartilage

Deborah Burstein

Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) was first described in 1996 as a nondestructive technique for quantitative measurements of glycosaminoglycan (GAG) concentration in articular cartilage samples [1]. Its translation to clinical platforms as a means of interrogating the molecular aspects of cartilage was demonstrated in 1997 with illustrative examples of apparent molecular degeneration in cartilage that was grossly intact morphologically [2]. Since then, over 150 reports of dGEMRIC involving in vitro and clinical studies have been published. These reports demonstrate the potential for molecular imaging techniques to illustrate new paradigms in the understanding of cartilage disease. However, along with the expanded applications come questions regarding appropriate protocols, possible sources of measurement and interpretation errors, and insight into directions for future study. This chapter describes the theoretical basis of dGEMRIC, protocols, pitfalls, and opportunities, focusing on the clinical aspects. Further details can be found in several reviews [3–7].

Biophysical Basis for dGEMRIC

dGEMRIC, like most biochemical methods for measuring cartilage GAG including radiotracer, histology with cationic dyes, and biochemical assays, is based on biophysical principles elucidated by Maroudas almost 40 years ago [8]. These principles rely on the fact that GAG is the source of the majority of the fixed charge on the cartilage extracellular matrix, due to the abundant carboxyl and sulfate groups on the GAG molecules. Mobile ions will distribute in tissue according to the GAG (negative fixed charge) concentration. The associated theories can be used to calculate the concentration of GAG based on the concentration of the mobile ion in the tissue. In dGEMRIC the mobile ion is the MRI contrast agent $Gd\text{-}DTPA^{2-}$ (Gadopentetate Dimeglumine, Bayer Health Care).

If $Gd\text{-}DTPA^{2-}$ is allowed time to equilibrate in tissue, theoretically the concentration of $Gd\text{-}DTPA^{2-}$ can be determined from a measurement of the MRI parameter T1 in the presence of $Gd\text{-}DTPA^{2-}$ (T1(Gd)), and the concentration of GAG can then be calculated from the determined concentration of the mobile $Gd\text{-}DTPA^{2-}$ ion. In practice, the conditions for quantitation of absolute GAG are not met in clinical studies due to the contrast agent not being in steady state with the cartilage, and the relative distribution of T1 (Gd) is utilized as a metric for the relative distribution of cartilage GAG, as described below.

D. Burstein (✉)
Department of Radiology, Beth Israel Deaconess Medical Center, 4 Blackfan Circle, Boston, MA, USA
e-mail: dburstei@bidmc.harvard.edu

Protocol Considerations and Pitfalls

In order to determine the GAG concentration in cartilage from the concentration of Gd-DTPA^{2-}, Gd$-$DTPA^{2-} needs to be added to the system, and it needs time to penetrate the cartilage (which may take up to several hours in the avascular tissue). T1 measurements are then needed in order to assess the distribution of Gd-DTPA^{2-} concentration. There are several protocol considerations with respect to these steps:

T1 pre-contrast

Theoretically, calculation of Gd-DTPA^{2-} requires knowledge of T1 both before and after contrast agent administration. However, under some conditions the variation of T1 without contrast across the tissue in an individual, or between individuals, may be small enough relative to the changes induced by the contrast agent that it is possible to utilize the T1 post-contrast alone as a metric of Gd-DTPA^{2-} concentration. This has generally been found to be the case in dGEMRIC studies of native cartilage tissue of the knee, hip, and finger [9–12].

Administration of Gd-DTPA^{2-}

In clinical studies, the Gd-DTPA^{2-} is administered either by intra-articular or intravenous injection. Early studies demonstrated that in the thick cartilage of the patella of the knee, the kinetics of penetration of Gd-DTPA^{2-} was faster with intravenous administration due to its penetration from both the synovial and bone surfaces [2]. However, this may be less of an issue for the thinner cartilages of other aspects of the knee or of the hip.

An advantage of the intra-articular injection is the improved delineation of cartilage in addition to the dGEMRIC effect [13, 14]. However, intravenous is generally easier to implement and thus has been utilized in the majority of dGEMRIC studies to date of the knee, although a number of recent studies have utilized intra-articular injections for dGEMRIC of the hip [13–16].

Dose

Increasing dosage of Gd-DTPA^{2-} results in easier delineation of differences in GAG, as well as lower T1(Gd) and hence faster T1(Gd) measurement. Offsetting this is the concern for the safety issues of contrast agent at higher doses [17]. The majority of dGEMRIC studies have been done with "double dose" Gd-DTPA^{2-} (0.2 mmol/kg), although utility of single dose has also been illustrated [18].

Another consideration with dosing is that, since adipose tissue does not take up Gd-DTPA^{2-} as much as lean mass, dosing by weight results in individuals with higher BMI given an effectively larger dose of Gd-DTPA^{2-} [19]. Therefore, in studies including subjects with a large range of BMI, one can either adjust the dose, or "correct" the dGEMRIC values post-acquisition [19]. The BMI effect will not be an issue for longitudinal studies of individuals where BMI does not change during the study period. Alternatively, studies of relative dGEMRIC values within the knee at one time or across time will demonstrate effects apparent in localized regions of the knee even if BMI changes might be of concern [20].

Delay Period

Once injected, the Gd-DTPA^{2-} needs time to penetrate into the cartilage. Early studies demonstrated that 30–90 min were effective for penetration into hip cartilage, and 2–3 h into all the cartilages of the knee [21]. In particular, thicker cartilage would require a longer time for contrast agent penetration, and incomplete penetration of contrast in thick cartilage may result in higher T1(Gd) than would be obtained after longer equilibration times [22]. Therefore, early loss of GAG in thick cartilage may be underrepresented by this technique. Potentially offsetting the effect of longer penetration time in thick

cartilage and overestimation of the GAG concentration is the effect of faster penetration kinetics of contrast agent into degraded tissue [23].

The faster penetration of Gd-DTPA^{2-} into degraded cartilage also implies that earlier time points after contrast agent injection will result in a larger observed effect difference between healthy and diseased tissue [24] as the Gd-DTPA^{2-} will enter degraded tissue faster and will go to a higher concentration [25], and then wash out faster [26].

In interpreting clinical studies and clinical trials, the time after injection should be taken into account and consistency of this time noted. Most hip studies have been done with a delay time of about 30 min after injection; most knee studies have been done after 90 min.

Joint Motion

The initial clinical studies demonstrated that some form of motion of the joint is necessary for consistent penetration of the Gd-DTPA^{2-} into cartilage [21]. The protocols for this motion have varied from walking 10 min, to climbing stairs, to passive motion of the joint. No definitive study has yet been undertaken to define whether one type of motion is better than another.

T1 Imaging

Although T1 weighted images might demonstrate areas depleted of cartilage [2], quantitation of T1(Gd) allows for an absolute index for direct comparison across people and time points.

Calculated images of T1 can be obtained through some form of inversion recovery or saturation recovery pulse sequence. The most straightforward, although also the most time-consuming, are standard 2D inversion recovery pulse sequences. These are generally limited by the number of sections that can be imaged in a reasonable imaging time, and therefore are appropriate if a given section of the joint is of interest and can be localized to easily from scout scans.

More generally, three-dimensional pulse sequences allow for coverage of the joint and post-processing of the region of interest. This is particularly of value with the relatively spherical geometry of the hip joint. A number of studies have validated 3D T1 imaging compared to 2D sequences [27–31], and low versus high resolution imaging [32].

After the imaging data are obtained, calculated T1 maps are made through a number of software packages available. In general the data are reported as mean T1(Gd) from a region of interest.

An additional consideration for the hip is the visualization of T1(Gd) along the natural anatomic zones of the hip cartilage. In this regard, a number of studies have reported the radial distribution of T1(Gd) [33–35].

Field Strength

Both 1.5T and 3T are commonly used for musculoskeletal imaging applications. While generally 3T would have advantages in terms of achievable resolution, the higher T1 values at 3T result in a longer imaging time for dGEMRIC at that field strength. In addition, B1 inhomogeneity, which can be a factor in the accuracy of T1 measurements, is more problematic at 3T than at 1.5T. Correction schemes for B1 inhomogeneity have recently been proposed [36–38]. Pilot studies have also recently been reported at 7 T [39].

Combination with Other Pulse Sequences

A number of parameters have been proposed for interrogating the molecular aspects of cartilage, as discussed in other chapters in this book. There have been several proposals to utilize combined information from several parameters, which raises the issue of whether they can be measured in one scan session.

Since T2 is much more sensitive to tissue macromolecules than to Gd-DTPA^{2-}, T2 is not significantly impacted by Gd-DTPA^{2-}, and it is possible to measure both T2 and dGEMRIC after administration of Gd-DTPA^{2-} [40, 41]. This is not true for T1rho, which would be strongly affected by the concentration of Gd-DTPA^{2-}. Therefore, combined measures of T1rho and dGEMRIC would require imaging both before and after contrast agent administration.

The accuracy of cartilage thickness or volume measurements in the presence of Gd-DTPA^{2-} has been investigated for knee cartilage. Baseline measurements were found to be comparable with or without the contrast agent in the tissue [42]; however, a later study found that changes in thickness over time yielded disparate results depending on whether the measurements were made in the presence of Gd-DTPA^{2-} [43]. Improved accuracy may be a matter of optimizing the segmentation routines for post-Gd-DTPA^{2-} tissue contrast, and/or improving inherent errors in the volume measurement themselves.

Reproducibility of T1 Measurements

Reproducibility of studies needs to be interpreted in the context of the level of changes that need to be evaluated for a given study. Measurements of reproducibility of dGEMRIC are also complicated by the kinetics of the contrast agent washing in and out of cartilage. Due to the contrast agent administration, two complete studies immediately following one another are also not appropriate. Therefore, many of the reproducibility studies have been done with scans several weeks apart, and the results are a combination of actual measurement reproducibility and variation in the natural levels of cartilage molecular composition over these short time frames.

With this in mind, the reproducibility data can be evaluated. Early studies showed a reproducibility of about 15 % in the knee [21]. This has been improved with faster pulse sequences and better analysis routines. In the knee, the

reproducibility has been shown to be between 5 and 8 % depending on the size of the regions of interest [44], while in the hip similar values were obtained (3.7–6.8 %) [45]. Interobserver variability in drawing standardized regions of interest was found to be better than 3 % in the different compartments of the knee [46]. Image registration was found to improve the reproducibility in the knee with ICC ranging from 0.85 to 0.9 [47, 48].

Since many of the clinically observed variations within a joint, between people, or changes over time are on the order of 20 % and higher (see sections below), the reported reproducibility values are sufficient for many applications.

Validation Studies

The theories developed by Maroudas [8] assume that the cartilage is in equilibration with a large "bath" (surrounding source) of the mobile ion, in this case Gd-DTPA^{2-}. These conditions are relatively easily achieved in vitro by placing the cartilage sample in a solution containing Gd-DTPA^{2-} for several hours, and a number of bench studies have validated the concentration of GAG as determined by dGEMRIC against biochemical and histological metrics [1, 49].

In clinical studies, the conditions of equilibrium and infinite bath surrounding the tissue do not hold. Therefore, the relative distribution of GAG within a joint, and between individuals, is inferred from the T1(Gd) maps. These distributions measured in vivo have compared well to histology from samples obtained after the imaging from total knee replacement surgeries [49]. Another means of validating the clinical dGEMRIC studies is to compare T1(Gd) images obtained with Gd-DTPA^{2-} to those obtained with a nonionic contrast agent. A small study initially demonstrated that the T1 distribution after administration of a nonionic contrast agent was uniform, compared with the "lesions" seen in the presence of Gd-DTPA^{2-} [2].

Opportunities

Within the context of the protocol and interpretation issues described above, the ability to distinguish molecular characteristics of morphologically intact tissue has the potential to greatly enhance our understanding of cartilage physiology and disease and impact therapeutic planning and evaluation. The majority of dGEMRIC studies have been in the knee and hip, although there are a number of reports of dGEMRIC applied to the finger joints [12, 50–52] and ankle [53]. dGEMRIC protocols have also been applied in the meniscus [54–56] and intervertebral discs [57, 58]; however, the considerations of transport are much more of a concern in these thick tissues, and the interpretation of the studies is likely to be different than those in the articular cartilages.

Applications of dGEMRIC in the hip will be described in detail in a later chapter; here we briefly present evidence for general types of opportunities that have been demonstrated in the hip as well as other joints that might be applicable to the hip in future studies.

Cartilage Physiology and Pathophysiology

While imaging studies tend to focus on disease, a better understanding of physiology might lead to lifestyle changes or interventions that might prevent degeneration of the joint. For example, adherence to an exercise regimen was shown to increase the dGEMRIC Index [48, 59, 60]. Similarly, in obese subjects, quadriceps strength was shown to correlate positively with dGEMRIC [61], as did weight loss [20]. The implication of biomechanics in alterations in molecular metrics is further strengthened by the observation that knee malalignment has been shown to correlate to medial/lateral ratios of the dGEMRIC Index [62]. Similarly, different types of femoroacetabular impingement had different distributions of dGEMRIC across the hip [63]. The observations regarding the impact of

biomechanics may provide a window for therapeutics such as modifying the mechanical tissue conditions.

Pre-radiographic Disease

The most straightforward application of dGEMRIC or any molecular imaging technique is simply to demonstrate and follow "lesions" in otherwise apparently normal-appearing cartilage. Detection and monitoring of these lesions demonstrate a number of paradigm-changing concepts in the evaluation of cartilage physiology and pathophysiology. In particular, molecular scans such as dGEMRIC have demonstrated "lesions" or generally low values in radiographically normal compartments [51, 62, 64], which has implications for the enrollment of such individuals as "controls" in natural history or intervention trials for cartilage disease.

The prior reliance on radiographic abnormalities which only progress has led to the paradigm that arthritis only progresses with worsening disease. The observation of molecular level lesions in radiographically normal or stable states also allows for monitoring of regression as well as progression of disease or injury. In one case report, a posterior cruciate ligament injury was found to result in a dGEMRIC decrease over the first month but then a return to baseline after several months of rehabilitation [65].

Prediction of Disease Progression, Regression, or Success of Intervention

A determination of the molecular status of cartilage might enable one to predict whether the joint is progressing towards worse disease, improving in status, or whether the cartilage is in sufficiently good state such that an intervention can be effective.

One study showed that low dGEMRIC values preceded radiographic OA [66], and another showed that decreasing dGEMRIC in chronic rheumatoid arthritis despite treatment, leading to joint replacement [67]. Similarly several

studies have shown the negative impact of ACL injuries, exacerbated by meniscal injuries [68, 69]. Conversely, there are examples of studies demonstrating protective effects, such as muscle strength in knees with meniscal injuries [70] and collagen hydrolysate over a period of 6 months [71].

Summary

Molecular imaging of cartilage has the potential to improve understanding of joint disease, and the evaluation of protective and interventional procedures. dGEMRIC was designed as a method of measuring the GAG component of cartilage. Certain protocol considerations must be taken into account, and data interpretation in relation to actual GAG content needs to consider the nonequilibrium state of contrast distribution in vivo. With these considerations, changes in the dGEMRIC index have been used to compare cartilage status across individuals and monitor cartilage status over time for a given individual. In total, these studies have illustrated the dynamic, responsive, reversible nature of cartilage molecular structure, and hence the potential to impact cartilage health with lifestyle and therapeutic interventions.

References

1. Bashir A, Gray ML, Burstein D. Gd-DTPA2- as a measure of cartilage degradation. Magn Reson Med. 1996;36:665–73.
2. 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;205:551–8.
3. Gray ML, Burstein D, Kim YJ, Maroudas A. 2007 Elizabeth Winston Lanier Award Winner. Magnetic resonance imaging of cartilage glycosaminoglycan: basic principles, imaging technique, and clinical applications. J Orthop Res. 2008;26:281–91.
4. Crema MD, Roemer FW, Marra MD, Burstein D, Gold GE, Eckstein F, Baum T, Mosher TJ, Carrino JA, Guermazi A. Articular cartilage in the knee: current MR imaging techniques and applications in clinical practice and research. Radiographics. 2011;31: 37–61.
5. Dahlberg A, Lammentausta E, Tiderius CJ, Nieminen MT. In vivo monitoring of joint cartilage—lessons to be learned by delayed gadolinium enhanced magnetic resonance imaging of cartilage. Eur Musculoskelet Rev. 2012;7:58–62.
6. Burstein D. Tracking longitudinal changes in knee degeneration and repair. J Bone Joint Surg. 2009;91 Suppl 1:51–3.
7. Burstein D, Gray M, Mosher T, Dardzinski B. Measures of molecular composition and structure in osteoarthritis. Radiol Clin North Am. 2009;47: 675–86.
8. Maroudas A. Physicochemical properties of articular cartilage. In: Freeman M, editor. Adult articular cartilage. London: Pitman Medical; 1979. p. 215–90.
9. Williams A, Mikulis B, Krishnan N, Gray M, McKenzie C, Burstein D. Suitability of T(1GD) as the dGEMRIC index at 1.5T and 3.0T. Magn Reson Med. 2007;58:830–4.
10. Li W, Du H, Scheidegger R, Wu Y, Prasad PV. Value of precontrast T(1) for dGEMRIC of native articular cartilage. J Magn Reson Imaging. 2009;29:494–7.
11. Bittersohl B, Hosalkar HS, Kim YJ, Werlen S, Siebenrock KA, Mamisch TC. Delayed gadolinium-enhanced magnetic resonance imaging (dGEMRIC) of hip joint cartilage in femoroacetabular impingement (FAI): are pre- and postcontrast imaging both necessary? Magn Reson Med. 2009;62:1362–7.
12. Buchbender C, Scherer A, Kropil P, Korbl B, Quentin M, Reichelt D, Lanzman RS, Mathys C, Blondin D, Bittersohl B, Zilkens C, Hofer M, Wittsack HJ, Schneider M, Antoch G, Ostendorf B, Miese F. Cartilage quality in rheumatoid arthritis: comparison of T2* mapping, native T1 mapping, dGEMRIC, deltaR1 and value of pre-contrast imaging. Skeletal Radiol. 2012;41:685–92.
13. Boesen M, Jensen KE, Qvistgaard E, Danneskiold-Samsoe B, Thomsen C, Ostergaard M, Bliddal H. Delayed gadolinium-enhanced magnetic resonance imaging (dGEMRIC) of hip joint cartilage: better cartilage delineation after intra-articular than intravenous gadolinium injection. Acta Radiol. 2006; 47:391–6.
14. Kwack KS, Cho JH, Kim MM, Yoon CS, Yoon YS, Choi JW, Kwon JW, Min BH, Sun JS, Kim SY. Comparison study of intraarticular and intravenous gadolinium-enhanced magnetic resonance imaging of cartilage in a canine model. Acta Radiol. 2008; 49:65–74.
15. Bittersohl B, Hosalkar HS, Kim YJ, Werlen S, Trattnig S, Siebenrock KA, Mamisch TC. T1 assessment of hip joint cartilage following intra-articular gadolinium injection: a pilot study. Magn Reson Med. 2010;64:1200–7.
16. 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;45:538–42.

17. Abujudeh HH, Kaewlai R, Kagan A, Chibnik LB, Nazarian RM, High WA, Kay J. Nephrogenic systemic fibrosis after gadopentetate dimeglumine exposure: case series of 36 patients. Radiology. 2009; 253:81–9.

18. Nojiri T, Watanabe N, Namura T, Narita W, Ikoma K, Suginoshita T, Takamiya H, Komiyama H, Ito H, Nishimura T, Kubo T. Utility of delayed gadolinium-enhanced MRI (dGEMRIC) for qualitative evaluation of articular cartilage of patellofemoral joint. Knee Surg Sports Traumatol Arthrosc. 2006;14:718–23.

19. Tiderius C, Hori M, Williams A, Sharma L, Prasad PV, Finnell M, McKenzie C, Burstein D. dGEMRIC as a function of BMI. Osteoarthritis Cartilage. 2006;14:1091–7.

20. Anandacoomarasamy A, Leibman S, Smith G, Caterson I, Giuffre B, Fransen M, Sambrook PN, March L. Weight loss in obese people has structure-modifying effects on medial but not on lateral knee articular cartilage. Ann Rheum Dis. 2012;71:26–32.

21. Burstein D, Velyvis J, Scott KT, Stock KW, Kim YJ, Jaramillo D, Boutin RD, Gray ML. Protocol issues for delayed Gd(DTPA)(2-)-enhanced MRI (dGEMRIC) for clinical evaluation of articular cartilage. Magn Reson Med. 2001;45:36–41.

22. Hawezi ZK, Lammentausta E, Svensson J, Dahlberg LE, Tiderius CJ. In vivo transport of Gd-DTPA(2-) in human knee cartilage assessed by depth-wise dGEMRIC analysis. J Magn Reson Imaging. 2011;34:1352–8.

23. Gillis A, Gray M, Burstein D. Relaxivity and diffusion of gadolinium agents in cartilage. Magn Reson Med. 2002;48:1068–71.

24. Salo EN, Nissi MJ, Kulmala KA, Tiitu V, Toyras J, Nieminen MT. Diffusion of Gd-DTPA(2)(−) into articular cartilage. Osteoarthritis Cartilage. 2012; 20:117–26.

25. Tiderius CJ, Jessel R, Kim YJ, Burstein D. Hip dGEMRIC in asymptomatic volunteers and patients with early osteoarthritis: the influence of timing after contrast injection. Magn Reson Med. 2007;57:803–5.

26. Tiderius CJ, Olsson LE, Leander P, Ekberg O, Dahlberg L. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) in early knee osteoarthritis. Magn Reson Med. 2003;49:488–92.

27. Kimelman T, Vu A, Storey P, McKenzie C, Burstein D, Prasad P. Three-dimensional T1 mapping for dGEMRIC at 3.0 T using the look locker method. Invest Radiol. 2006;41:198–203.

28. McKenzie CA, Williams A, Prasad PV, Burstein D. Three-dimensional delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 1.5T and 3.0T. J Magn Reson Imaging. 2006;24:928–33.

29. Li W, Scheidegger R, Wu Y, Vu A, Prasad PV. Accuracy of T1 measurement with 3-D look-locker technique for dGEMRIC. J Magn Reson Imaging. 2008;27:678–82.

30. Mamisch TC, Dudda M, Hughes T, Burstein D, Kim YJ. Comparison of delayed gadolinium enhanced MRI of cartilage (dGEMRIC) using inversion recovery and fast T1 mapping sequences. Magn Reson Med. 2008;60:768–73.

31. Szumowski J, Durkan MG, Foss EW, Brown DS, Schwarz E, Crawford DC. Signal polarity restoration in a 3D inversion recovery sequence used with delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC). J Magn Reson Imaging. 2012;35(5):1248–55.

32. Sur S, Mamisch TC, Hughes T, Kim YJ. High resolution fast T1 mapping technique for dGEMRIC. J Magn Reson Imaging. 2009;30:896–900.

33. Bittersohl B, Steppacher S, Haamberg T, Kim YJ, Werlen S, Beck M, Siebenrock KA, Mamisch TC. Cartilage damage in femoroacetabular impingement (FAI): preliminary results on comparison of standard diagnostic vs delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC). Osteoarthritis Cartilage. 2009;17:1297–306.

34. Bittersohl B, Hosalkar HS, Werlen S, Trattnig S, Siebenrock KA, Mamisch TC. dGEMRIC and subsequent T1 mapping of the hip at 1.5 tesla: normative data on zonal and radial distribution in asymptomatic volunteers. J Magn Reson Imaging. 2011; 34:101–6.

35. Domayer SE, Mamisch TC, Kress I, Chan J, Kim YJ. Radial dGEMRIC in developmental dysplasia of the hip and in femoroacetabular impingement: preliminary results. Osteoarthritis Cartilage. 2010;18: 1421–8.

36. Siversson C, Tiderius CJ, Dahlberg L, Svensson J. Local flip angle correction for improved volume T1-quantification in three-dimensional dGEMRIC using the look-locker technique. J Magn Reson Imaging. 2009;30:834–41.

37. Lattanzi R, Glaser C, Mikheev AV, Petchprapa C, Mossa DJ, Gyftopoulos S, Rusinek H, Recht M, Kim D. A B1-insensitive high resolution 2D T1 mapping pulse sequence for dGEMRIC of the HIP at 3 tesla. Magn Reson Med. 2011;66:348–55.

38. Siversson C, Chan J, Tiderius CJ, Mamisch TC, Jellus V, Svensson J, Kim YJ. Effects of B1 inhomogeneity correction for three-dimensional variable flip angle T1 measurements in hip dGEMRIC at 3 T and 1.5 T. Magn Reson Med. 2012;67:1776–81.

39. Welsch GH, Mamisch TC, Hughes T, Zilkens C, Quirbach S, Scheffler K, Kraff O, Schweitzer ME, Szomolanyi P, Trattnig S. In vivo biochemical 7.0 tesla magnetic resonance: preliminary results of dGEMRIC, zonal T2, and T2* mapping of articular cartilage. Invest Radiol. 2008;43:619–26.

40. Nieminen MT, Menezes NM, Williams A, Burstein D. T2 of articular cartilage in the presence of Gd-DTPA2. Magn Reson Med. 2004;51:1147–52.

41. Taylor C, Carballido-Gamio J, Majumdar S, Li X. Comparison of quantitative imaging of cartilage for osteoarthritis: T2, T1rho, dGEMRIC and contrast-

enhanced computed tomography. Magn Reson Imaging. 2009;27:779–84.

42. Eckstein F, Buck RJ, Wyman BT, Kotyk JJ, Le Graverand MP, Remmers AE, Evelhoch JL, Hudelmaier M, Charles HC. Quantitative imaging of cartilage morphology at 3.0 tesla in the presence of gadopentate dimeglumine (Gd-DTPA). Magn Reson Med. 2007;58:402–6.

43. Eckstein F, Wyman BT, Buck RJ, Wirth W, Maschek S, Hudelmaier M, Le Graverand MP. Longitudinal quantitative MR imaging of cartilage morphology in the presence of gadopentetate dimeglumine (Gd-DTPA). Magn Reson Med. 2009; 61:975–80.

44. Multanen J, Rauvala E, Lammentausta E, Ojala R, Kiviranta I, Hakkinen A, Nieminen MT, Heinonen A. Reproducibility of imaging human knee cartilage by delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 1.5 tesla. Osteoarthritis Cartilage. 2009;17:559–64.

45. Bittersohl B, Hosalkar HS, Haamberg T, Kim YJ, Werlen S, Siebenrock KA, Mamisch TC. Reproducibility of dGEMRIC in assessment of hip joint cartilage: a prospective study. J Magn Reson Imaging. 2009;30:224–8.

46. Tiderius CJ, Tjornstrand J, Akeson P, Sodersten K, Dahlberg L, Leander P. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC): intra- and interobserver variability in standardized drawing of regions of interest. Acta Radiol. 2004;45:628–34.

47. Bron EE, van Tiel J, Smit H, Poot DH, Niessen WJ, Krestin GP, Weinans H, Oei EH, Kotek G, Klein S. Image registration improves human knee cartilage T1 mapping with delayed gadolinium-enhanced MRI of cartilage (dGEMRIC). Eur Radiol. 2013;23(1): 246–52.

48. Van Ginckel A, Baelde N, Almqvist KF, Roosen P, McNair P, Witvrouw E. Functional adaptation of knee cartilage in asymptomatic female novice runners compared to sedentary controls. A longitudinal analysis using delayed gadolinium enhanced magnetic resonance imaging of cartilage (dGEMRIC). Osteoarthritis Cartilage. 2010;18:1564–9.

49. Bashir A, Gray ML, Hartke J, Burstein D. Nondestructive imaging of human cartilage glycosaminoglycan concentration by MRI. Magn Reson Med. 1999;41:857–65.

50. Williams A, Shetty SK, Burstein D, Day CS, McKenzie C. Delayed gadolinium enhanced MRI of cartilage (dGEMRIC) of the first carpometacarpal (1CMC) joint: a feasibility study. Osteoarthritis Cartilage. 2008;16:530–2.

51. Miese F, Buchbender C, Scherer A, Wittsack HJ, Specker C, Schneider M, Antoch G, Ostendorf B. Molecular imaging of cartilage damage of finger joints in early rheumatoid arthritis with delayed gadolinium-enhanced magnetic resonance imaging. Arthritis Rheum. 2012;64:394–9.

52. Miese F, Kropil P, Ostendorf B, Scherer A, Buchbender C, Quentin M, Lanzman RS, Blondin D, Schneider M, Bittersohl B, Zilkens C, Jellus V, Ch Mamisch T, Wittsack HJ. Motion correction improves image quality of dGEMRIC in finger joints. Eur J Radiol. 2011;80:e427–31.

53. Domayer SE, Trattnig S, Stelzeneder D, Hirschfeld C, Quirbach S, Dorotka R, Nehrer S, Pinker K, Chan J, Mamisch TC, Dominkus M, Welsch GH. Delayed-gadolinium-enhanced MRI of cartilage in the ankle at 3 T: feasibility and preliminary results after matrix-associated autologous chondrocyte implantation. J Magn Reson Imaging. 2010;31:732–9.

54. 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 Rheum. 2007;56:1507–11.

55. Mayerhoefer ME, Welsch GH, Riegler G, Mamisch TC, Materka A, Weber M, El-Rabadi K, Friedrich KM, Dirisamer A, Trattnig S. Feasibility of texture analysis for the assessment of biochemical changes in meniscal tissue on T1 maps calculated from delayed gadolinium-enhanced magnetic resonance imaging of cartilage data: comparison with conventional relaxation time measurements. Invest Radiol. 2010;45:543–7.

56. Mayerhoefer ME, Mamisch TC, Riegler G, Welsch GH, Dobrocky T, Weber M, Apprich S, Scheurecker G, Szomolanyi P, Puchner S, Trattnig S. Gadolinium diethylenetriaminepentaacetate enhancement kinetics in the menisci of asymptomatic subjects: a first step towards a dedicated dGEMRIC (delayed gadolinium-enhanced MRI of cartilage)-like protocol for biochemical imaging of the menisci. NMR Biomed. 2011;24:1210–5.

57. Vaga S, Brayda-Bruno M, Perona F, Fornari M, Raimondi MT, Petruzzi M, Grava G, Costa F, Caiani EG, Lamartina C. Molecular MR imaging for the evaluation of the effect of dynamic stabilization on lumbar intervertebral discs. Eur Spine J. 2009;18 Suppl 1:40–8.

58. Vaga S, Raimondi MT, Caiani EG, Costa F, Giordano C, Perona F, Zerbi A, Fornari M. Quantitative assessment of intervertebral disc glycosaminoglycan distribution by gadolinium-enhanced MRI in orthopedic patients. Magn Reson Med. 2008; 59:85–95.

59. Tiderius CJ, Svensson J, Leander P, Ola T, Dahlberg L. dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) indicates adaptive capacity of human knee cartilage. Magn Reson Med. 2004;51:286–90.

60. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. Arthritis Rheum. 2005;52:3507–14.

61. Anandacoomarasamy A, Giuffre BM, Leibman S, Caterson ID, Smith GS, Fransen M, Sambrook PN, March LM. Delayed gadolinium-enhanced magnetic resonance imaging of cartilage: clinical associations in obese adults. J Rheumatol. 2009;36:1056–62.

62. Williams A, Sharma L, McKenzie CA, Prasad PV, Burstein D. Delayed gadolinium-enhanced magnetic resonance imaging of cartilage in knee osteoarthritis: findings at different radiographic stages of disease and relationship to malalignment. Arthritis Rheum. 2005;52:3528–35.

63. Mamisch TC, Kain MS, Bittersohl B, Apprich S, Werlen S, Beck M, Siebenrock KA. Delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) in femoacetabular impingement. J Orthop Res. 2011;29:1305–11.

64. Pollard TC, McNally EG, Wilson DC, Wilson DR, Madler B, Watson M, Gill HS, Carr AJ. Localized cartilage assessment with three-dimensional dGEMRIC in asymptomatic hips with normal morphology and cam deformity. J Bone Joint Surg. 2010;92:2557–69.

65. Young AA, Stanwell P, Williams A, Rohrsheim JA, Parker DA, Giuffre B, Ellis AM. Glycosaminoglycan content of knee cartilage following posterior cruciate ligament rupture demonstrated by delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC). A case report. J Bone Joint Surg. 2005;87:2763–7.

66. Owman H, Tiderius CJ, Neuman P, Nyquist F, Dahlberg LE. Association between findings on delayed gadolinium-enhanced magnetic resonance imaging of cartilage and future knee osteoarthritis. Arthritis Rheum. 2008;58:1727–30.

67. Tiderius CJ, Sandin J, Svensson J, Dahlberg LE, Jacobsson L. Knee cartilage quality assessed with dGEMRIC in rheumatoid arthritis patients before and after treatment with a TNF inhibitor. Acta Radiol. 2010;51:1034–7.

68. Fleming BC, Oksendahl HL, Mehan WA, Portnoy R, Fadale PD, Hulstyn MJ, Bowers ME, Machan JT, Tung GA. Delayed gadolinium-enhanced MR imaging of cartilage (dGEMRIC) following ACL injury. Osteoarthritis Cartilage. 2010;18:662–7.

69. Neuman P, Tjornstrand J, Svensson J, Ragnarsson C, Roos H, Englund M, Tiderius CJ, Dahlberg LE. Longitudinal assessment of femoral knee cartilage quality using contrast enhanced MRI (dGEMRIC) in patients with anterior cruciate ligament injury–comparison with asymptomatic volunteers. Osteoarthritis Cartilage. 2011;19:977–83.

70. Ericsson YB, Tjornstrand J, Tiderius CJ, Dahlberg LE. Relationship between cartilage glycosaminoglycan content (assessed with dGEMRIC) and OA risk factors in meniscectomized patients. Osteoarthritis Cartilage. 2009;17:565–70.

71. McAlindon TE, Nuite M, Krishnan N, Ruthazer R, Price LL, Burstein D, Griffith J, Flechsenhar K. Change in knee osteoarthritis cartilage detected by delayed gadolinium enhanced magnetic resonance imaging following treatment with collagen hydrolysate: a pilot randomized controlled trial. Osteoarthritis Cartilage. 2011;19:399–405.