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dGEMRIC as a function of BMI[1]

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Summary

Objective: Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) reflects cartilage glycosaminoglycan (GAG) distribution. The technique assumes that the plasma levels of the contrast agent Gd-DTPA^{2-} are the same across individuals after intravenous (IV) injection, when dosing by weight. However, adipose tissue has lower extracellular water (ECW) than lean tissue. The aims of this study were to measure (1) plasma Gd-DTPA^{2-} levels vs body mass index (BMI), and (2) dGEMRIC vs BMI after correcting for the dose–BMI effect.

Method: (1) Plasma Gd-DTPA^{2-} levels were analyzed at 3–90 min after IV injection per body weight in 24 individuals with BMI between 21.5 and 46.5. (2) dGEMRIC was compared with BMI in 19 asymptomatic volunteers and 23 with osteoarthritis (OA).

Results: (1) Plasma Gd-DTPA^{2-} kinetics were similar in obese and non-obese groups, however, overall concentration was higher in the obese group. A very obese subject (BMI 45) would have 1.4 times higher Gd-DTPA^{2-} concentration than a lean subject (BMI 20), which translates into a bias in dGEMRIC of up to 20%. (2) With dose bias taken into account, dGEMRIC showed no correlation with BMI in asymptomatic knees. In OA knees, unnarrowed femoral compartments demonstrated a negative correlation between dGEMRIC and BMI ($R = 0.57$, $P = 0.004$). No correlation was seen in radiographically narrowed compartments.

Conclusion: BMI can be a source of dosing bias in dGEMRIC and a correction factor should be considered in cross-sectional studies with a large range of BMI. There is no correlation between dGEMRIC and BMI in asymptomatic knees, but a negative correlation in OA knees.

Key words: Cartilage, Articular/pathology, Gadolinium DTPA, Glycosaminoglycans, MR Imaging/diagnosis, Osteoarthritis, Body mass index, Proteoglycans.

Introduction

Obesity is a well-known risk factor for osteoarthritis (OA), the most prevalent joint disease in society[1,2]. The ability to measure the relationship between obesity and the molecular structure of cartilage would improve our understanding of the relationship between obesity and OA. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) may provide a means to assess the relationship of obesity and cartilage glycosaminoglycan (GAG) content non-invasively. Several preliminary studies have previously investigated dGEMRIC as a means of delineating cartilage molecular quality in OA[3–6].

In the dGEMRIC technique, the negatively charged contrast agent Gd-DTPA^{2-} (Magnevist, Berlex, NJ) is injected intravenously and diffuses into articular cartilage, with a final concentration inversely proportional to the cartilage GAG concentration[7]. The relative GAG concentration is estimated by measuring the T1 values after penetration of the contrast agent (T1(Gd)). The mean T1(Gd) within a clinically relevant region of articular cartilage is usually referred to as the dGEMRIC Index[6].

In the current dGEMRIC protocol, Gd-DTPA^{2-} is administered per kilogram body weight with the assumption that the distribution volume of the contrast agent is proportional to body weight. However, because Gd-DTPA^{2-} is distributed solely in the extracellular water (ECW), and since lean tissue has approximately twice the ECW content per unit weight as adipose tissue[8], it was recently suggested that different body compositions between individuals might result in a dosing bias with corresponding bias in the dGEMRIC Index[9]. Therefore, before studying the effects of obesity with dGEMRIC, it is important to evaluate the impact of different body compositions in dosing of the contrast agent.

In the present study we examine (1) plasma Gd-DTPA^{2-}-concentration after an intravenous (IV) injection with dosing by weight in individuals with a wide range of body mass indices (BMIs), and (2) the correlation between the dGEMRIC Index and BMI both before and after dose correction in asymptomatic subjects and subjects with OA.

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Patients and methods

PART 1, PLASMA Gd-DTPA^{2-} CONCENTRATION VS BMI

Twenty-four subjects of varying BMI (Mean 30, range 21–47) were included in the study. BMI was defined as (body weight, kg)/(height, m)^2. The study was approved by the Institutional Review Board and a written informed consent was obtained from all subjects. Three milliliters of blood were drawn pre-contrast and at 15, 30, 45, 60, and 90 min after an IV injection of Gd-DTPA^{2-} at 0.2 mM/kg of body weight. In 10 subjects (five obese, five non-obese, where obese is defined as BMI $\geq$ 30), blood was obtained at additional early time-points (3, 5 and 10 min) after the injection in order to compare the plasma time course curves between obese and non-obese subjects. In five individuals, the experiment was repeated for reproducibility at intervals ranging from 9 to 11 months.

Blood samples were centrifuged, and the plasma separated and stored at $-20\,^{\circ}$C. For each measurement, samples were brought to room temperature prior to measurements. The plasma Gd-DTPA^{2-} concentration was determined by MR Spectroscopy using an 8.5 T magnet (Bruker Instruments, Billerica, MA). T1 for each plasma sample was calculated using ParaVision curve fitting software (Bruker Biospin, Billerica, MA). In 12 of the plasma samples, the Gd-DTPA^{2-} concentration was also analyzed by high-resolution inductively coupled plasma atom emission spectrometry (ICP, Elemental Analysis, Lexington, KY). The correlation between ICP and MR Spectroscopy measurements for Gd-DTPA^{2-} concentration was excellent ($R^2 = 0.99$). All data reported here are from the MR Spectroscopy.

In some of the first subjects investigated, where blood was drawn from the same arm as the injection, unrealistically high values of plasma Gd-DTPA^{2-} were found at 15 min post-injection, indicating contamination of Gd-DTPA^{2-} in the IV catheter. The protocol was therefore changed after the first 12 subjects to drawing blood from the opposite arm as the IV injection. All of the 10 individuals whose samples were used for the early time point analysis had blood drawn from the opposite arm as injection.

PART 2, dGEMRIC vs BMI

dGEMRIC of the knee joint cartilage was performed on one knee in each of 20 asymptomatic volunteers (BMI 18–43, Mean: 26 ± 6) and in 23 subjects with OA (BMI 22–39, Mean: 28 ± 4). Institutional Review Board approval was obtained, and all participants gave informed consent. Subjects with knee OA were recruited from the Mechanical Factors in Arthritis of the Knee (MAK) study. As previously described, the MAK subjects had symptomatic knee OA as defined by the presence of knee pain on most days of the past month[10]. dGEMRIC analyses from this cohort were previously reported relating dGEMRIC to radiographic indices[6].

dGEMRIC scans were performed on 1.5 T General Electric Sigma Excite scanners equipped with TwinSpeed gradients (GE Healthcare, Waukesha, WI) approximately 90 min after an IV injection of Gd-DTPA^{2-} at 0.2 mmol/kg body weight. dGEMRIC was acquired by either 2-D or 3-D sequence. Single slice sagittal 2-D dGEMRIC images were acquired using an Fast spin echo inversion recovery (FSE IR) sequence with five inversion delays ranging from 50 to 1680 ms, recovery time/echo time (TR/TE) = 1800/14 ms. Medial and lateral sections from the knee were imaged sequentially. Three-dimensional images were acquired using an inversion recovery-prepared fast spoiled gradient-recalled acquisition in the steady state sequence with a 20° flip angle. Five inversion delays were collected with variable time between inversion pulses[11]. Inversion times ranged from 28 ms to 1650 ms, with a TR ranging from 300 ms to 1950 ms. The 3-D slab was oriented sagittally. In the asymptomatics, 32 slices (3 mm thick) were acquired with 625×625-μm in-plane resolution; bandwidth (BW) was ± 42 kHz. In OA patients imaged as a subset of the MAK study[6], 28 slices (3 mm thick) were acquired with 364×364 μm in-plane resolution; BW $\pm$ 31.2 kHz.

T1 maps were generated with a pixel-by-pixel three-parameter fit routine using Matlab (The MathWorks, Natick, MA). Two sagittal sections from each knee were considered, one each from the center of the medial and lateral condyles. In the OA subjects, the femoral compartments were labeled as "narrowed" or "unnarrowed" based on the joint space narrowing score on radiographs. The 23 subjects assessed in this report are a subset of a larger cohort of subjects imaged by dGEMRIC and previously reported[6]. In order to assess inter-subject variation, only the subset of subjects who had one narrowed and one unnarrowed femoro-tibial compartment was considered for this study. dGEMRIC Indices were calculated in the central weight-bearing femoral cartilage (cFC) (the region most prone to early cartilage degeneration[12,13]), and also in the non-weight bearing posterior femoral cartilage (pFC) and the tibial plateau cartilage (TP), for a total of three region of interest (ROIs) per section. In one asymptomatic knee, the dGEMRIC Index could not be determined from one condyle due to motion artifact thus yielding a total of 117 dGEMRIC Indices in asymptomatic volunteers. In nine ROIs from seven OA subjects a valid dGEMRIC Index could not be determined due to extreme cartilage thinning. Thus, a total of 129 dGEMRIC Indices were examined in the OA subjects.

The dGEMRIC Index was calculated both with and without correcting for the dose bias according to the results of the plasma analysis in Part 1. The correction was done by calculating the expected difference in plasma Gd-DTPA^{2-} level for each individual based on his/her BMI, relative to the plasma Gd-DTPA^{2-} level of an individual with BMI 20. Differences in plasma Gd-DTPA^{2-} levels across people are referred to as the "dose bias". The T1(Gd) measurement was then corrected to the value it would have if the plasma Gd-DTPA^{2-} level was reduced by an amount equivalent to the estimated dose bias. BMI correction calculations are detailed in the Appendix.

STATISTICAL ANALYSIS

Linear regression analysis was used to describe the correlation between BMI and Gd-DTPA^{2-} concentration and between BMI and the dGEMRIC Index. Friedman repeated measures analysis of variance (ANOVA) on ranks was used to compare the Gd-DTPA^{2-} concentration over time in obese vs non-obese individuals. Coefficient of variation in percent (C.V.%) was used to describe the intra-individual variability of repeated analysis of Gd-DTPA^{2-} concentration. C.V.% was calculated as the standard deviation of measurement 1 – measurement $2/\sqrt{2}$ in percent of the mean value.

Results

PART 1, PLASMA Gd-DTPA^{2-} CONCENTRATION VS BMI

From the 10 subjects, five obese and five non-obese, investigated with multiple time sampled points, the decay

in plasma Gd-DTPA^{2-} concentration was plotted as a function of time (Fig. 1). The plasma concentration was higher in the obese (BMI: 37 ± 6) than in the non-obese (BMI: 26 ± 3) individuals, $P < 0.001$. The difference in plasma concentration between the two groups was between 20% and 25% at all time-points, indicating a similar plasma elimination rate in obese and non-obese subjects.

CORRELATION BETWEEN BMI AND Gd-DTPA^{2-} CONCENTRATION

Figure 2 shows the correlation between BMI and plasma [Gd-DTPA^{2-}] from all 24 subjects using the data from blood sampling 60 min post-injection, $R = 0.58$, $P = 0.003$. The equation of the regression line is: $y = 0.0075x + 0.366$. Calculating from this regression line, the plasma [Gd-DTPA^{2-}] of an individual with BMI 45 is 1.36 times higher than the plasma [Gd-DTPA^{2-}] of an individual with BMI 20, 60 min after the IV injection.

There was a similar positive correlation between BMI and Gd-DTPA^{2-} concentration at all time-points post-injection of 15, 45, 60, and 90 min with R values ranging from 0.54 to 0.71 ($P < 0.05$ to $P < 0.001$). Thus similar ratios (between 1.32 and 1.41) for [Gd-DTPA^{2-}] for an individual with BMI 45 to an individual with BMI 20 were found at all post-injection intervals examined.

REPRODUCIBILITY

In three of the five subjects whose blood was drawn from the same arm into which the contrast media were injected, repeated analyses of plasma Gd-DTPA^{2-} showed unrealistically high Gd-DTPA^{2-} at the 15-min analysis indicating contamination of Gd-DTPA^{2-} in the catheter. Consequently, the reproducibility in these five individuals was low at 15 min with a C.V.% of 52%. However, at 30 min and beyond, when no contrast medium was residing in the catheter the reproducibility was very good with a C.V.% of 1.8%, 2.4%, 3.2% and 3.4% at 30, 45, 60 and 90 min, respectively.

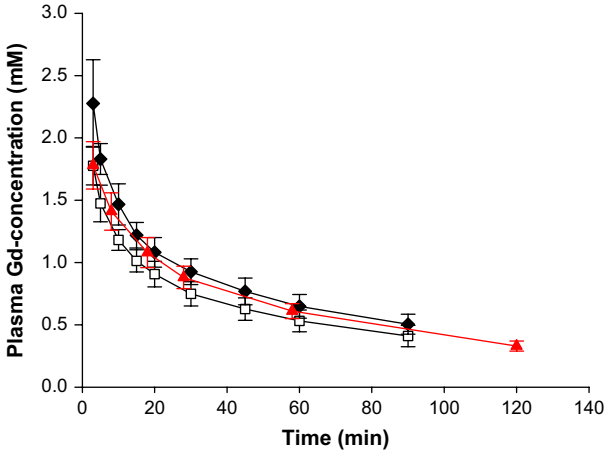

Fig. 1. Gadolinium concentration in plasma over time in (closed diamonds) five obese (Mean BMI: 37) and (open squares) five non-obese (Mean BMI: 26) individuals. The concentration was higher in the obese subjects ($P < 0.001$) but the relative difference between the two groups was similar over time indicating similar elimination rates. The data agree well with prior data (in red) reported by Weinmann *et al.*[17].

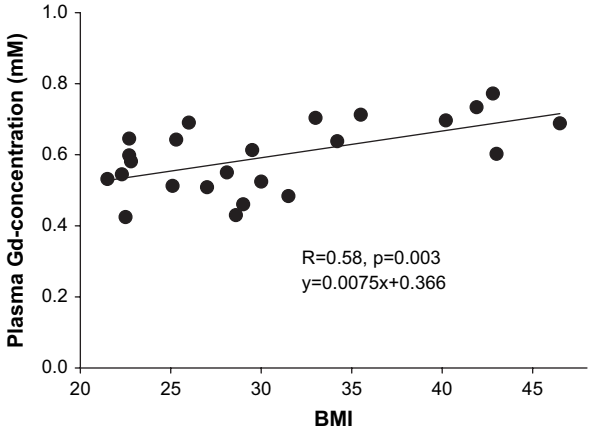

Fig. 2. Correlation between BMI and [Gd-DTPA^{2-}] at 60 min post-injection, $R = 0.58$, $P = 0.003$. The equation of the regression line, $y = 0.0075x + 0.366$, is used to calculate dosing bias between individuals with different BMI.

PART 2, dGEMRIC VS BMI

Uncorrected asymptomatic data (Fig. 3) demonstrate a negative correlation between the dGEMRIC Index and BMI in both the medial ($R = 0.574$, $P = 0.01$) and lateral ($R = 0.464$, $P = 0.04$) cFC. There was no correlation between the dGEMRIC Index and BMI in asymptomatics in either the medial or the lateral cFC after correcting for dose bias. Other compartments (posterior condyle and tibial plateau) showed no significant correlation either before or after dose correction, although both the medial pFC and TP showed a trend (not significant) towards a positive slope after correction.

Figure 4(a) shows negative correlations between the dGEMRIC Index and BMI in unnarrowed cFC compartments of subjects with OA both without and with correction for dose bias ($R = 0.686$, $P < 0.001$; $R = 0.571$, $P = 0.004$, respectively). Similar trends were seen in the other regions of unnarrowed compartments. While a correlation existed before correction, no correlation between the dGEMRIC Index and BMI was seen in the narrowed compartment after dose correction [Fig. 4(b)].

Discussion

The positive correlation between Gd-DTPA^{2-} concentration and BMI after an IV injection with dosing by weight indicates a dosing bias in the present dGEMRIC protocol. Comparing a subject with BMI 45 (very obese) to another individual with BMI 20 (lean), the obese person may have close to 40% higher plasma Gd-DTPA^{2-} concentration after an IV injection. This dosing bias is presumably due to the lower ECW fraction in adipose vs lean tissue[8]. A previous study directly measured ECW as a function of BMI[14]. In that study, non-obese women with an average BMI of 21.2 were found to have 21% ECW relative to the body weight, whereas obese women with BMI of 46.9 had 16% ECW. Assuming a linear relationship between %ECW and Gd-DTPA^{2-} concentration after IV injection, this would give a higher concentration with a factor of 1.3 in the obese compared to the non-obese women, and thus the results of the current study are consistent with the earlier study.

While a correlation existed between plasma Gd-DTPA^{2-} and BMI, there was a fair amount of scatter in the curve.

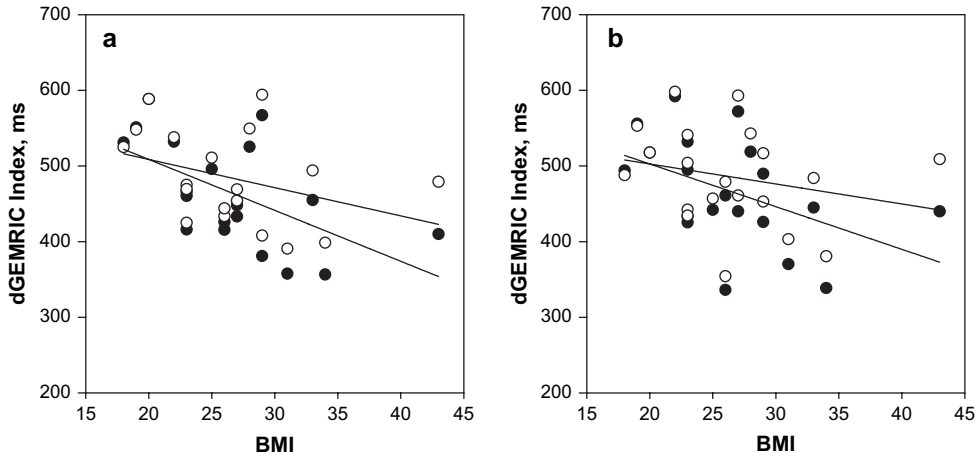

Fig. 3. Correlation between the dGEMRIC Index and BMI in asymptomatic subjects before (shaded circles) and after (open circles) dose bias correction in (a) medial and (b) lateral cFC. The lines represent best-fit linear regression analyses. No significant correlation was found after correction for dose bias.

The good reproducibility between repeated plasma spectroscopy measurements of the same individuals indicates that the range of Gd-DTPA^{2-} concentrations that we observe within a certain BMI-interval (Fig. 2) is due to inter-individual, and not to intra-individual variability or to spectroscopic measurement error. The variability between individuals may relate to different body compositions despite similar BMI. In this regard, BMI is only a predictor of obesity where, for example, variations in muscle composition are not taken into account[15,16].

The elimination rate of Gd-DTPA^{2-} that we found is consistent with data previously reported by Weinmann *et al.*[17] (Fig. 1). The absolute values of the five healthy volunteers who were included in that study were in between those of the obese and non-obese subjects of the present study, despite that a higher dose was used in the prior study (0.25 mmol/kg body weight). The BMI of the individuals in the earlier study was not reported, and may explain the difference in absolute values of the curves.

Dose bias will be an issue in dGEMRIC where there is a large range of BMI within a given study and absolute comparisons are made between individuals. It will also be an issue in longitudinal studies where patients may follow a treatment for losing weight and the BMI changes significantly over the time course of the study. In these cases, either dosing by BMI instead of weight can be applied, or the data need to be post-process corrected. In the extreme cases of BMI differences, a 40% higher Gd-DTPA^{2-} concentration results in approximately 20% lower dGEMRIC Index (see Appendix for details).

There are a number of situations in which dose bias will not be a factor. In longitudinal studies where BMI does not change significantly, the dose bias will be present at all time-points and percent changes with an intervention will not be affected[18]. Dose bias will also not be an issue where different compartments are compared within a knee[6,19]. Dose correction may not impact studies not related to BMI *per se*; in retrospectively correcting for dose bias in a recently published study of dGEMRIC compared with radiography in this same cohort[6], none of the conclusions regarding dGEMRIC vs radiographic metrics of OA were altered.

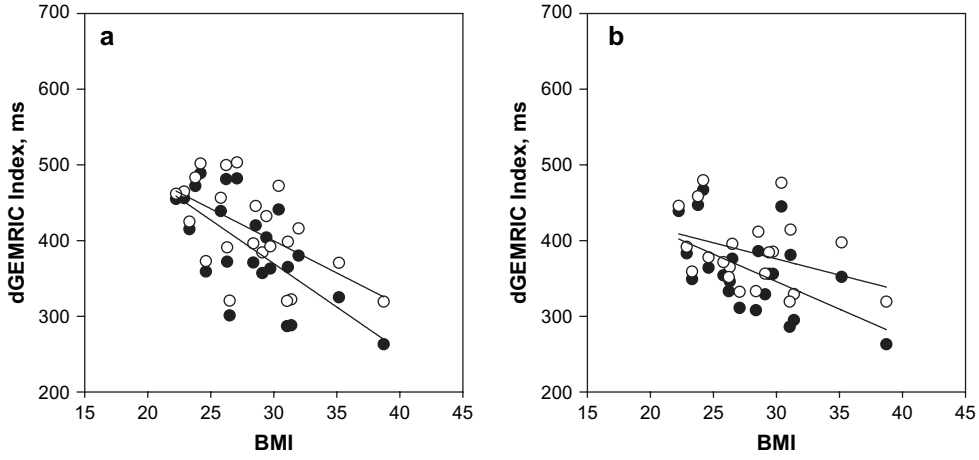

Fig. 4. Correlation between the dGEMRIC Index and BMI in OA subjects before (shaded circles) and after (open circles) dose bias correction in unnarrowed (a) and narrowed (b) compartments. The lines represent best-fit linear regression analyses. There is a strong negative correlation between the dGEMRIC Index and BMI in unnarrowed compartments that persists after correction for dose bias.

There were no significant correlations between dGEMRIC and BMI in asymptomatic subjects. After correcting for dose bias, there was a trend for a positive correlation in the posterior medial condyle, which might be an indication of upregulated metabolism in healthy joints with increased mechanical loads. However, this observation could also be the result of "over-correcting" the dGEMRIC Indices given some of the assumptions that needed to be incorporated into the correction scheme (Appendix).

In the unnarrowed compartments of OA subjects, there was a negative correlation between dGEMRIC and BMI even after compensating for a dosing bias. The results are consistent with lower cartilage GAG content with increasing BMI, and may predict progression to more severe disease in heavier individuals. This has also been the conclusion in longitudinal studies of patients with knee OA that were assessed with conventional radiographs[20,21]. It can be speculated that the chondrocytes are unable to maintain GAG levels under the increased mechanical stress of increased weight in the diseased joint. In support of this hypothesis, it was recently shown that overweight is associated with lower GAG content in patients at high risk of developing knee OA; in 46 meniscectomized patients, there was a strong negative correlation between the dGEMRIC Index and BMI ($R = 0.5$, $P < 0.001$) approximately 4 years after the meniscectomy[11].

In cases where the joint space is already narrowed, no correlation between dGEMRIC and BMI was observed in our study. This may be due to a "floor effect", as the dGEMRIC values in the narrowed compartments were relatively low across this cohort. This further illustrates that dGEMRIC may be most valuable in early stages of OA, before joint space narrowing is present[4].

The correction scheme employed several assumptions that need to be verified in further studies; in particular the relaxivity assumed for cartilage *in vivo* at 1.5 T. However, note that since Fig. 4(a and b) represent data from different compartments in the same knees, the dose bias could not account for the different correlations seen with BMI.

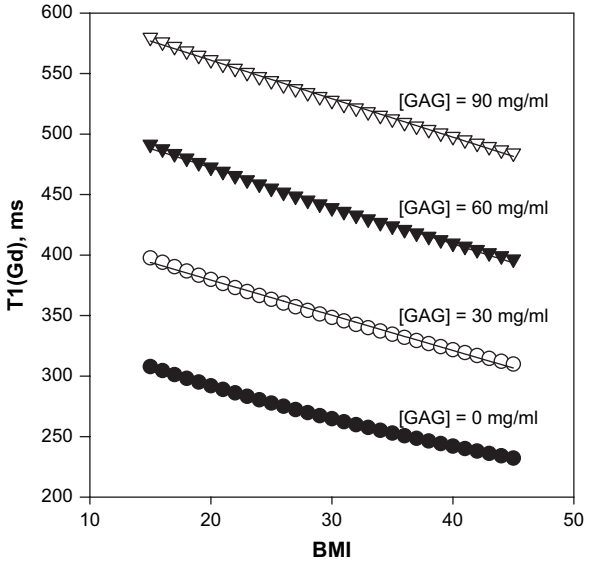

Fig. 5. Bias in T1(Gd) as a result of Gd-DTPA^{2-} dose bias. For a given GAG level, T1(Gd) should be constant across BMI if dose bias was not present. The graph shows the variation in T1(Gd) due to dose bias for [GAG] = 0 (shaded circles), 30 (open circles), 60 (shaded triangles), and 90 (open triangles) mg/ml. The slopes of the regression lines are nearly the same across a wide range of GAG levels: $m = -2.5$, -2.9, -3.1, and -3.2 ms/BMI, respectively.

In summary, it has been demonstrated that individuals with higher BMI will receive a higher effective blood plasma dose of Gd-DTPA^{2-} than individuals with lower BMI. The effect on the dGEMRIC Index can be important in cases where cross-sectional comparisons are done with cohorts exhibiting a range of BMI. In other studies, such as longitudinal evaluation of changes within individuals, the dose effect will not impact the findings. The dose bias can be compensated for by redesigning the dGEMRIC protocol to dose by BMI, or by post-process correction of the dGEMRIC Indices. A negative correlation between dGEMRIC and BMI was detected in OA knees, but not in asymptomatic knees. These findings deserve further study to better understand the time course and factors involved in molecular degeneration of cartilage in degenerative joint disease, and its association with BMI.

Appendix

The data presented in Fig. 2 of this report demonstrate a relationship between blood plasma Gd-DTPA^{2-} concentration and BMI, when all individuals are given Gd-DTPA^{2-} doses by weight:

$$[\text{Gd-DTPA}^{2-}]_{\text{plasma}} = 0.0075\text{BMI} + 0.366. \quad (1)$$

The dGEMRIC technique assumes that all individuals have the same plasma Gd-DTPA^{2-} concentration after injection; therefore, a correction factor needs to be applied to dGEMRIC data to account for the bias in blood Gd-DTPA^{2-} levels with BMI.

The following derives the correction that can be made to calculate the T1(Gd) for an individual to compensate for the higher plasma Gd-DTPA^{2-} level relative to an individual with BMI = 20 (as a reference BMI).

The T1(Gd) value of cartilage tissue can be calculated using the standard relaxivity equation and cartilage parameters:

$$\text{T1(Gd)} = 1/([\text{Gd-DTPA}^{2-}]_{\text{tissue}} r + (1/\text{T1o})) \quad (2)$$

where r = relaxivity = 4.7 (mmol × s)$^{-1}$, and T1o = T1 without Gd-DTPA^{2-} = 1000 ms [Ref. 22]. To our knowledge, the value of cartilage T1 relaxivity *in vivo* at 1.5 T in the presence of Gd-DTPA^{2-} is not known. Here we have estimated it from previously reported *in vitro* values and measured temperature dependence. After equilibration with Gd-DTPA^{2-}, Gillis *et al.* found T1 relaxivity in bovine cartilage explants at 2 T to range from 5.18 to 6.28 (mmol × s)$^{-1}$ at room temperature[23]. The *in vitro* temperature dependence measured by Rozijn *et al.*, was found to be -0.087 (mmol × s × °C)$^{-1}$ [Ref. 24]. To estimate *in vivo* relaxivity, we averaged Gillis' room temperature values and used Rozijn's relationship to adjust for a 12°C temperature increase to body temp (5.73 (mmol × s)$^{-1}$ + (-0.087 (mmol × s × °C)$^{-1}$) × 12°C = 4.7(mmol × s)$^{-1}$). This estimate is reasonable given that Gd-DTPA^{2-} T1 relaxivity measured in whole blood at 37°C at 1.5 T has been reported to range from 4.0 to 4.6 (mmol × s)$^{-1}$ [Ref. 25]. Since relaxivity increases with macromolecular content, its value in cartilage tissue can be expected to be somewhat higher than that in blood.

$Gd\text{-}DTPA^{2-}_{tissue}$ can be related to $Gd\text{-}DTPA^{2-}_{plasma}$ by rearranging the equation for the distribution of a charged ion in a charged matrix[7]:

$$[Gd\text{-}DTPA^{2-}]_{tissue} = \left\{ \frac{FCD\sqrt{\left[Gd\text{-}DTPA^{2-}\right]_{plasma}}}{4\left[Na^{+}\right]_{plasma}} + \sqrt{\left(\frac{FCD^{2}\sqrt{\left[Gd\text{-}DTPA^{2-}\right]_{plasma}}}{16\left[Na^{+}\right]^{2}_{plasma}} + \left[Gd\text{-}DTPA^{2-}\right]_{plasma} \right)} \right\}^{2}. \quad (3)$$

Here the FCD is the fixed charge density of the cartilage, related to GAG concentration by:

$$FCD,\ mM = (-2\ \text{charges/GAG}) \times ([GAG],\ mg/ml)/(0.5025\ mg/mol). \quad (4)$$

For a constant GAG concentration, the $Gd\text{-}DTPA^{2-}_{tissue}$, and hence T1(Gd), should be constant across individuals if their $Gd\text{-}DTPA^{2-}_{plasma}$ levels are constant. The variation of T1(Gd) due to varying $Gd\text{-}DTPA^{2-}_{plasma}$ concentration with BMI can be approximated by combining the relationship between BMI and $Gd\text{-}DTPA^{2-}_{plasma}$ (Eq. 1) with the relationships between [GAG], $Gd\text{-}DTPA^{2-}_{plasma}$, and $Gd\text{-}DTPA^{2-}_{tissue}$ (Eqs. 3 and 4) and the relationship between $Gd\text{-}DTPA^{2-}_{tissue}$ and T1(Gd) (Eq. 2). The result is an estimate of T1(Gd) as a function of BMI for a given GAG concentration. This function is plotted in Fig. 5 for different GAG levels. The slopes of the regression lines are nearly the same across a wide range of GAG levels ($m = -2.5$, -2.9, -3.1, and -3.2 ms/BMI, for [GAG] = 0, 30, 60, and 90 mg/ml, respectively); therefore we can write the "corrected" T1 to that of an individual with BMI = 20 as:

$$T1(\text{corrected}) = T1(\text{measured}) + 3(BMI - 20) \quad (5)$$

where the slope was corrected for T1 values given in ms.

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