Dosing bias in dGEMRIC due to BMI differences

C. J. Tiderius[1], A. Williams[1], M. Hori[1], M. Finnell[2], L. Sharma[3], P. Prasad[4], D. Burstein[1]

[1]Department of Radiology, Beth Israel Deaconess Medical Center, Boston, MA, United States, [2]Department of Rheumatology, Beth Israel Deaconess Medical Center, Boston, MA, United States, [3]Feinberg School of Medicine, Northwestern University, Chicago, IL, United States, [4]Department of Radiology, Evanston Northwestern Healthcare, Evanston, IL, United States

Introduction:

In delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), the negatively charged contrast agent Gd-DTPA^{2-} is injected intravenously and diffuses into articular cartilage, with a final concentration inversely proportional to the to the cartilage gycosaminoglycan (GAG) concentration [1]. The GAG content is estimated by measuring the T1 values after penetration of the contrast agent ($T1_{Gd}$). In the current protocol, Gd-DTPA^{2-} is administered per kilogram of body weight with the assumption that the distribution volume is proportional to body weight. However, because Gd-DTPA^{2-} is distributed mainly into the extracellular water (ECW), and the percentage of ECW is lower in adipose tissue compared with lean tissue [2], subjects with a high body fat content may receive a higher effective dose of Gd-DTPA^{2-}, which would be misinterpreted as a lower GAG content than actually exists. Since obesity is a risk factor of osteoarthritis (OA), it is of particular importance to identify a potential dosing bias in subjects of different body composition. The goal of this study was to establish the correlation between plasma [Gd-DTPA^{2-}] and BMI and apply the results to clinical dGEMRIC measurements.

Methods:

Part 1: 3 ml of blood was obtained pre-contrast and at 15, 30, 45, 60, and 90 minutes after an IV injection of Gd-DTPA^{2-} (Magnevist, Berlex, NJ) at 0.2mM/kg of body weight in 23 volunteers with BMI 22-47 (mean 30±7). In 9 of those subjects, blood was obtained at additional early time-points (3, 5 and 10 minutes) after the injection in order to evaluate the elimination curve of the contrast medium. In 5 individuals, the experiment was repeated for reproducibility. Each blood sample was centrifuged and plasma [Gd-DTPA^{2-}] was analyzed by MR spectroscopy at 8.5 T.

Part 2: dGEMRIC data were previously reported on 19 asymptomatic volunteers (BMI 18-43, Mean: 27±6) and 30 OA patients (BMI 22-39, Mean = 29±4) [3, 4]. The effect of correcting for dose bias was evaluated by calculating the percentage increase in plasma [Gd-DTPA^{2-}] for each individual based on BMI, relative to an individual with BMI 20. The $T1_{Gd}$ measurement was then corrected to the value it would have if the Gd-DTPA^{2-} dose was reduced by that percent.

Results:

Part 1: Fig 1 shows the decay in plasma [Gd-DTPA^{2-}] as a function of time in 4 obese (mean BMI: 35±5) and 5 non-obese (mean BMI: 25±3) subjects. The concentration was higher in the obese compared with the non-obese subjects, $p<0.01$. However, the elimination rate was similar in both groups, indicating that the concentration bias is not time-dependant. Furthermore, there was a positive correlation between [Gd-DTPA^{2-}] and BMI at all times, e.g. R=0.61, p=0.002 at 60 minutes (Fig 2). The fair amount of scatter within a certain BMI range indicates other sources of variability in plasma [Gd-DTPA^{2-}], such as percent adipose tissue not being represented well by BMI, different renal clearance rates, etc.. The reproducibility was very good with C.V.% between 2-3% at 30, 45, 60 and 90 minutes, and therefore the scatter cannot be explained by experiment error or intra-individual variability.

Part 2: Figures 3a and b show previously reported data from an asymptomatic and an OA population [3, 4] after correcting for BMI dose bias. dGEMRIC does not have a correlation with BMI in asymptomatics, but still maintains a strong negative correlation in unnarrowed compartments of OA knees (R= 0.5, $p<0.002$, Fig 3b).

Discussion:

- The positive correlation between BMI and plasma [Gd-DTPA^{2-}] indicates the potential for a dosing bias in the dGEMRIC protocol. In comparing two individuals with extreme differences in BMI of 45 and 20, the individuals with extremely high body fat content (BMI 45) may have as much as 40% higher plasma [Gd-DTPA^{2-}] than individuals with extremely low body fat (BMI 20), which translates to a 20% lower dGEMRIC Index than would be obtained if the same GdDTPA plasma concentration had been achieved as with the low BMI case.
- 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 [5]. Dose bias will also not be an issue where different compartments are compared within a knee [4, 6].
- Dose bias will be an issue where there is a large range of BMI within a given study and comparisons are made between individuals. In this case, either dosing by BMI instead of weight can be applied, or the data need to be post-process corrected. Assumptions of the correction algorithm need to be further examined.
- Correcting for dose bias did not change any previously reported conclusions regarding dGEMRIC versus radiographic metrics of OA [4].
- Even if the dose bias is corrected for, there is still a strong negative correlation between the dGEMRIC Index and BMI in OA subjects (Figure 3b). The implications of this regarding BMI as a risk factor for OA needs further study.

Figure 1

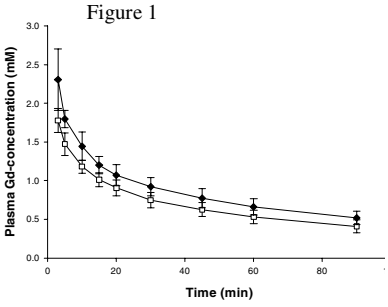

Figure 2

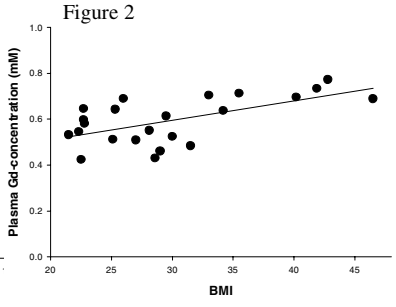

Figure 3a – asymptomatic

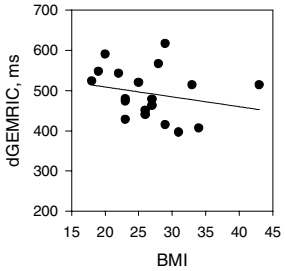

Figure 3b-OA

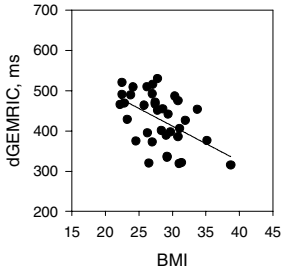

Figure 1 – Plasma [Gd-DTPA^{2-}] as a function of time in obese vs. non-obese subjects. Similar elimination rates in both groups indicate that the concentration bias is not time-dependant.

Figure 2 - Plasma [Gd-DTPA^{2-}] as a function of BMI 60 min after injection. The positive correlation (R=0.61, p=0.002) indicates the potential for BMI-dependant dosing bias in dGEMRIC.

Figure 3– Correlation between BMI and dGEMRIC index *after correction for dosing bias*. (a) No correlation is seen between the dGEMRIC Index and BMI in an asymptomatic population, but (b) there is a negative correlation seen between BMI and $T1_{Gd}$ in OA subjects (R=0.5, $p<0.002$).

References: [1] Burstein D, et al. Mag Reson Med 2001; 45: 36-41. [2] Waki M, et al. Am J Physiol 1991; 261: 199-203. [3] Williams A, et al. ISMRM 2005. [4] Williams A, et al. Arthritis Rheum 2005; 52 (11): 3528-35. [5] Roos E and Dahlberg L, Arthritis Rheum, 2005; 52 (11): 3507-14. [6] Tiderius C, et al. Arthritis Rheum, 2005; 52 (1): 120-7.