Author’s response to reviews

Title: Pre-contrast T1 and cartilage thickness as confounding factors in dGEMRIC when evaluating human cartilage adaptation to physical activity

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Response to reviewers for the manuscript “Pre-contrast T1 and cartilage thickness as confounding factors in dGEMRIC when evaluating human cartilage adaptation to physical activity”

Technical Comments:

Missing:

- List of Abbreviations

RESPONS: List of abbreviation has been added and the text has been updated accordingly.

Editor Comments:

Reviewer reports:

Atsuya Watanabe (Reviewer 1): Summary

The authors examined the influence of pre-contrast T1 and cartilage thickness when assessing knee joint cartilage quality with dGEMRIC. They found that cartilage pre-contrast T1 and thickness may be sources of error in dGEMRIC that should be considered when analyzing bulk values.
General comment

This study is interesting, and the text is mostly concise and clearly written.

Specific comments

Introduction

OK.

Materials and methods

Page 4, line 85

Please clarify the definition of "healthy" subject.

RESPONSE: The sentence has been changed to “In this retrospective study we included 17 volunteers from a previous study of healthy subjects, i.e. no history of knee injury or knee surgery, with different levels of physical activity [17].”

Page 4, line 98 - page 5, line 108

Was the selection of TIs (50, 100, 200, 400, 800 and 1600 ms) suitable to measure the pre-contrast T1 value?

RESPONSE: The inversion times can be optimized for a T1 value or range of T1 values to be measured. The present protocol was designed for subjects post CM-injection. Since, T1 is longer before CM injection, it would have been beneficial with an additional inversion times > 1600 ms. However, more TIs or longer TIs also extend the measurement time, which may increase the risk involuntary motion during the protocol. The use of one protocol for both pre CM and post CM measurement is therefore a compromise resulting in suitable but not optimized measurement procedure.

The following sentence is added in the discussion: “Another limitation is the T1 measurement protocol. Longer inversion times would have been more appropriate for the higher pre-contrast T1 in the cartilage. As a result the uncertainty of the measured pre-contrast T1 is expected to be larger than for the post-contrast T1.”

It is important to perform the post-contrast T1 measurement on the same slice position as that acquired for the pre-contrast T1 measurement. Did you select the exactly same slice? If yes, please provide the method how you chose the post-contrast slice corresponding to the pre-contrast slice previously acquired.
RESPONSE: The following text has been added to Methods:”Identical location of the two sagittal slices (one in the medial and one in the lateral femoral compartment) in-between scans were carefully selected by the MRI technician. In addition, the first author (Z.H.) investigated that the thickness of the cartilage within each ROI did not change in-between repeated scans.”

The local concentration of Gd-DTPA in the tissue is determined by using the following equation:

\[ \text{Gd-DTPA} = \frac{1}{r} \left( \frac{1}{T_1\text{post}} - \frac{1}{T_1\text{pre}} \right) \]

where \( r \) is the relaxivity of Gd-DTPA in the tissue and \( T_1 \) equals 1 divided by the longitudinal relaxation time. It might be interesting to evaluate the local concentration of Gd-DTPA in cartilage using this equation. (Radiology. 2006 Apr;239(1):201-8.)

RESPONSE: The description of how the CM concentration was left out by mistake. The following text has been added: “Estimated gadolinium concentrations for all regions of interest were calculated using the following formula:

\[ [\text{Gd}] = \frac{1}{T_1\text{Gd} - 1/T_1\text{pre}}/r_1, \]

where \( T_1\text{Gd} \) is the T1 value after contrast agent injection, \( T_1\text{pre} \) is the T1 value before Gd-DTPA- injection, and \( r_1 \) is the relaxivity of Gd-DTPA, for which the value 4.1 s\(^{-1}\)mM\(^{-1}\) measured in human plasma at 37\(^\circ\)C temperature was used.”

A double dose of Gd-DTPA- (0.2 mmol/kg of Gd-DTPA-) has been used in many studies of dGEMRIC. Do you think the concentration of Gd-DTPA- could affect the results?

RESPONSE: Using three different doses of Gd-DTPA- (single, double and triple), we have previously demonstrated a linear dose-response of gadolinium concentration in femoral knee cartilage after intravenous injection (Tiderius et al, Magnetic Resonance in Medicine, 46(6):1067-7, 2001). Hence, we can assume that the results would have been similar after the double dose. However, triple dose may increase the sensitivity of the method as indicated in the same paper by Tiderius.

Page 5, line 110 - 120

The segmentation of the thin cartilage can be difficult. Please provide the rationale or methodology for this cartilage segmentation. Was the segmentation performed by a single investigator?

RESPONSE: Segmentation of thin cartilage is indeed difficult. Therefore, the rationale and methodology for cartilage segmentation has been described in detail in a previous article:

Hawezi ZK, Lammentausta E, Svensson J, Dahlberg LE, Tiderius CJ.

The following text has been added:” The segmentation procedure has been described in detail previously [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 Dec;34(6):1352-8].”

Results
OK.

Discussion
OK.

Tables, & Figures
OK.

Tzu-Chieh Liao (Reviewer 2): This paper is well-written and good to read. Some suggestions are listed as follow.

Methods
Of all the subjects, only 2 subjects were female, and were in the same group. I would suggest mentioning gender as a limitation. Also, would the results be different if the females were not included? Females have thinner cartilage by nature.

RESPONSE: It may be argued that different gender may be a possible limitation in the present study. However, a previous meta analysis has demonstrated that dGEMRIC results do not differ between men and women (Dahlberg LE, et al. In vivo monitoring of joint cartilage - Lessons to be learned by delayed gadolinium enhanced Magnetic Resonance Imaging of cartilage. European Musculoskeletal Review. vol 7, issue 1, 58-62, 2012.). Figure below. The text above has been added to the discussion.

How are the segmentation performed? By one examiner? Was a reliability testing carried out prior? Given the cartilage layer is thin, and you further characterized into deep and superficial layer, I would anticipate some degrees of error.
RESPONSE The rationale and methodology for cartilage segmentation has been described in detail in a previous article:

Hawezi ZK, Lammentausta E, Svensson J, Dahlberg LE, Tiderius CJ.


The following text has been added to Methods:” The segmentation procedure has been described in detail previously [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 Dec;34(6):1352-8].”

and to Discussion:

“Due to the limited spatial resolution of the MR images, it is a challenging task to segment the different compartments of the cartilage. To reduce uncertainty all segmentation was performed by one single observer.”

It is not known if segmentation was performed on all slices? Or certain slices? How did you determine the border of segmentation (anatomically?) (i.e. WB vs NWB)

RESPONSE. In Methods it reads “Two sagittal slices were localized to cover the central part of the lateral and medial femoral condyle, respectively.” I.E two slices were obtained;

In the Analysis section it reads “In the sagittal plane, the central parts of both the medial and lateral femoral condyles were divided into two main segments (weight-bearing and non-weight-bearing)” I.E. only the slice covering the lateral condyle was analyzed.

All segmentation was performed manually on anatomical landmarks as described in 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 Dec;34(6):1352-8..

Please elaborate on the quantification of cartilage thickness. Is it the average thickness? Or the maximum?

RESPONSE. In Methods it reads “Three measurements in each segment of the femoral cartilage was performed and the mean value was calculated”.

I.E. it is the mean of three measurements, which is reported.

How is GD concentration measured? This is not mentioned

RESPONSE: The description of how the CM concentration was left out by mistake. The following text has been added: “Estimated gadolinium concentrations for all regions of interest were calculated using the following formula:

\[
[Gd] = \frac{(1/T1Gd - 1/T1pre)}{r1},
\]

where T1Gd is the T1 value after contrast agent injection, T1pre is the T1 value before Gd-DTPA2- injection, and r1 is the relaxivity of Gd-DTPA2-, for which the value 4.1 s⁻¹mM⁻¹ measured in human plasma at 37°C temperature was used.”

Description of Table 3 mentioned data for both superficial and deep regions, but the table only showed data on superficial region.

RESPONSE: The header of Table 3 is wrong. It should only read superficial regions.

The text has been changed “Gadolinium concentration for the superficial regions of interest for Non Weight-Bearing (NWB) and Weight-Bearing (WB) cartilage for exercise and sedentary groups, respectively.

Discussion

The discussion was relatively short. How were the results compared to the previous study (ref 17- elite vs sedentary)?

RESPONSE: We have added several paragraphs to the discussion as indicated from the answers above. However, the specific answer to question raised here, i.e. the results of this study is compared with elite vs sedentary is given in the first paragraph of the Discussion “In a previous dGEMRIC study using bulk (full-thickness) index values, we found higher dGEMRIC index interpreted as better cartilage quality in exercising compared to sedentary healthy volunteers [17]. To examine the impact of recently described confounding factors in dGEMRIC, we now have performed a detailed re-analysis of our data including T1T1 pre contrast and cartilage thickness measurements. Unexpectedly, T1 pre-contrast (native T1) was different for the exercise and sedentary groups; exercising individuals having longer native T1. This will influence the dGEMRIC index, which is the combined effect of native T1 and the shortening of T1 caused by the contrast agent. Hence, the exercising individuals in this study will get a higher dGEMRIC index, due to longer native T1 than sedentary individuals.”

Please provide one sentence of clinical significance.

RESPONSE: The following sentence has been added to the conclusion “This study provides important information that exercising individuals have thicker cartilage and higher native T1
than sedentary individuals. Both these factors influence post contrast T1 analysis which complicates the interpretation of dGEMRIC bulk results.”