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Quantitative measurement of cartilage volume is possible using two-dimensional magnetic resonance imaging data sets

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Abstract

PURPOSE—3D MRI scans are generally used for quantitative cartilage measurements in knee osteoarthritis. However, a great deal of MRI data is from 2D scans, often thought to be unsuitable for quantitative cartilage assessment. The goal of our study was to demonstrate that mLACS, a modified version of the LocalArea Cartilage Segmentation (LACS) method, could be used to measure cartilage volume on 2D MRI images.

METHODS—We studied 301 randomly selected subjects from the OA Biomarkers Consortium FNIH Study, a nested case-control study within the Osteoarthritis Initiative (OAI). The study comprised four subgroups based on radiographic and pain progression. We compared mLACS applied to 2D TSE scans to LACS on 3D DESS data. The Pearson's correlation coefficient was used to establish agreement between LACS and mLACS, standardized response means (SRMs) for responsiveness, and intra-class correlation coefficients (ICCs) to measure reader precision. Logistic regression in a case/control analysis was used to compare the clinical validity between the two methods.

RESULTS—We found $R^2 = 0.76$ for the correlation between LACS and mLACs. For LACS, the responsiveness was SRM = 0.49 compared to 0.39 for mLACS. The odds ratios for the primary case/control analyses were 1.62 for LACS and 1.78 for mLACS. The intra and inter reader reproducibility values for mLACS were ICC = 0.90 and 0.86, respectively.

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Acquisition of data – *Schaefer, Nikac, Lynch, Duryea*
Analysis and interpretation of data – *Schaefer, Lynch, Duryea*
Drafting the article or revising it critically for important intellectual content - *Schaefer, Nikac, Lynch, Duryea*
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Conflict of interest statement: The authors declare that they have no conflicting interests.

CONCLUSION—This study has demonstrated that a reproducible, responsive, and clinically valid quantitative measurement of cartilage volume can be made using 2D TSE scans with a modest loss of responsiveness compared to 3D scans.

Keywords

Osteoarthritis; Cartilage; Knee; Magnetic Resonance Imaging; Segmentation Software

Introduction

Magnetic resonance imaging (MRI) is an ideal modality for assessing multiple structures associated with the progression of knee osteoarthritis (OA) [1]. These include cartilage, bone marrow lesions, effusion synovitis, and the meniscus. Cartilage changes can be assessed with semi-quantitative scoring methods [2, 3], however such techniques are subjective and do not directly measure the actual amount of the cartilage loss. True changes in the volume and thickness of cartilage can be examined using "quantitative" software-based methods that segment (outline) the cartilage on the MRI image slices [4–6]. Previously, high-resolution three-dimensional (3D) scans with near isotropic voxel spacing have been used for this purpose since lower resolution two-dimensional (2D) scans, with slices spacing much greater than the in-plane pixel spacing, were not considered to have sufficient quality for quantitative cartilage assessment[7].

However, a great deal of MRI data from both clinical sources and research studies are from such 2D scans; assessment of these images could provide valuable data to support hypothesis-based research of knee OA if quantitative cartilage measurements methods could be applied. We have developed and validated the local-area cartilage segmentation (LACS) method[6], which measures cartilage volume change in a focused region of the medial femoral condyle. Based on a robust 3D coordinate system, the region is, in principle, consistent across different imaging subjects and time points. Since LACS does not require a full segmentation of the cartilage plate, we believed it could be applied to 2D MRI images where partial volume artifacts and other suboptimal image quality issues would preclude using conventional segmentation techniques.

Methods

Study design and cohort

We studied 301 of the 600 subjects from the OA Biomarkers Consortium FNIH Study (https://oai.epi-ucsf.org/datarelease/FNIH.asp), a nested case-control study within the Osteoarthritis Initiative (OAI). The OAI is a longitudinal cohort study of 4,796 subjects with or at risk for knee OA at the beginning of the study. Scans from the other half of the FNIH subjects were used to develop the method. An extensive imaging protocol is performed at 7 visits, baseline, 12 months, 24 months, 36 months, 48 months, 72 months, and 96 months, which includes knee radiographs and MRI at each time point.

Details of the OAI Biomarkers Consortium FNIH Study have been published elsewhere [8, 9]. The study uses a case/control design and includes 600 subjects in four subgroups based

on radiographic and pain progression[10]. We randomly selected 301 of the 600 subjects so that the subgroup frequency distribution exactly matched that of the full 600 subjects. The 301 subjects were distributed as follows:

Group 1: radiographic and pain progressors (n =97),

Group 2: radiographic-only progressors (n =52),

Group 3: pain-only progressors (n=52),

Group 4: no radiographic or pain progressors (n=100).

For the main analysis, we adhered to the case control definition of the OAI Biomarkers Consortium FNIH Study [https://oai.epi-ucsf.org/datarelease/FNIH.asp[8] where subjects in Group 1 are defined as cases and controls included subjects in the other three groups (2, 3, and 4). For secondary analyses, we investigated comparisons apart from the main analysis by individually comparing Groups 1, 2, and 3 with Group 4, and all subjects with radiographic progression (Group 1 and 2) to subjects without radiographic progression (Groups 3 and 4). Similarly we combined all patients with pain progression (Groups 1 and 3) and compared them to all patients without pain progression (Groups 2 and 4) and examined individual comparisons between each of Groups 1, 2, and 3 to Group 4. (no radiographic or pain progressors).

LACS Method

Once anatomical landmarks are established, the LACS method[11] selects a rectangular region on the medial femur and attempts an automated segmentation of the cartilage. The software presents the MRI slices and computer segmentations to a reader along with annotations that indicate the limits of the segmentation “rectangle”. The reader then makes any necessary edits to the computer drawn contours to ensure that the segmentation is correct within the rectangle.

The readings for this study were performed by (LS), the same reader as in our previous study[11]. We used sagittal turbo spin echo fat-suppressed (TSE FS) (0.357 × 0.357 × 3.0 mm, Repetition Time (TR) 3200 ms, Echo Time (TE) 30 ms) intermediate-weighted MRI scans at the baseline and 24-month visits. Images were acquired on Siemens 3.0T Trio scanners. More information about the OAI imaging protocol is given in a separate publication[12]. In our previous work with the 3D DESS pulse sequence[13], we found that the edge of the rectangular region was generally not perfectly aligned with the slice direction; inclusion of a given voxel in the measurement region was completely dependent on the coordinate system. In contrast, the modified 2DLACS method constrained the edges of the region to be parallel to the slice direction to mitigate the thick slices of the 2D pulse sequence compared to the 3D DESS so that a fixed number of slices was always used. We also studied the use of different numbers of 3 mm slices from 5 (15 mm) to 7 (21 mm). The software used the 2DLACS method to segment cartilage in the regions specified by the coordinate system and the reader (was provided with image analysis tools to make corrections where necessary. Measurements taken from the 2D TSE images using 2DLACS were compared to measurements taken from 3D scans in our previously published study of these same 301 knees [11].

Statistical Analysis

The primary goal of the study was to demonstrate that 2DLACS method could provide valid measurements of cartilage volume on 2D TSE MRI scans. Validation consisted of several components. First, we compared 2DLACS to 3D LACS cartilage volume using a Bland Altman plot and Pearson's correlation coefficient. Second we compared the responsiveness to change of the 2D and 3D methods using standardized response means (SRMs). Clinical validity was established using logistic regression with odds ratios (OR) and 95% confidence intervals (CI) as metrics. We assessed the association of change in cartilage volume with progression status using the case/control definitions. Each model was adjusted for age, sex, BMI, and race. ORs were calculated per 1 standard deviation loss of cartilage from baseline to 24 months. We also assessed inter and intra-reader reproducibility of 2DLACS on the baseline and 24 month scans of 20 subjects selected randomly from the 301 using intra-class correlation coefficients (ICCs) .

Results

The subjects were 62.8% female, 78.1% white, had an average age of 62.0±9.2 years, BMI of 30.2±4.6, baseline WOMAC score of 2.2±3.0, and had KL grades distributed as: KL1:14.6%, KL2:54.2%, KL3:31.2%. Figure 1 shows the comparison between the 2DLACS (using 7 slices) and 3D LACS; we also found a Pearson's $R^2 = 0.76$. The limits of agreement were ±271.6mm^3 and, as expected, a substantial bias of 275.5mm^3 is evident.

Table 1 provides the case/control results and data from an independent study[9]. In general 3D LACS outperformed 2DLACS but the difference was mostly unsubstantial. For the primary case/control analysis (Group 1 versus Groups 2, 3, and 4), the OR was slightly larger for 2DLACS than for LACS, 1.78 versus 1.62. The greatest difference between LACS and 2DLACS was seen for secondary analyses comparing Groups 2 and 4, radiographic versus neither radiographic nor pain progression. There was generally a slight reduction of the ORs for readings using 5 or 6 slices versus 7, however all measurements for a given comparison had overlapping confidence intervals. 2DLACS also compared similarly to the readings from the independent study.

The responsiveness for the 3D DESS LACS, TSE 2DLACS (7 slices), 2DLACS (6 slices) and 2DLACS (5 slices) was SRM = −0.49, −0.39, −0.38, and −0.37 respectively indicating some loss of responsiveness from LACS to 2DLACS and a very modest decrease when using fewer slices. The intra and inter reader reproducibility values were ICC = 0.90 and 0.86. The average reader time was less than 4 minutes per scan split approximately evenly between a skilled and an unskilled reader.

Discussion

This study has demonstrated that a reproducible, responsive, and clinically valid (based on the odds ratios from a case/control analysis) quantitative measurement of cartilage volume can be made using 2D TSE scans with large 3 mm slice spacing. While there is a modest loss of responsiveness, the method has potential for use in studies where 3D MRI data sets are not available or for research using retrospective clinical scans where 3D pulse sequences

are often not employed. For example, 2DLACS may provide a method to assess data from retrospective studies such as the METEOR Trial [14], where only 2D MRI are available. 2D LACS may also be valuable for prospective studies where it is desirable to reduce imaging costs and may have an eventual role in the clinical environment. Going forward, a single 2D scan could potentially be used to quantify several OA-related MRI features such as bone marrow lesions, effusion/synovitis, in addition to cartilage volume. With the coordinate system in place, and the fixed number of slices, the measured surface area is essentially the same for both visits of given knee since Volume = [surface area] × [average thickness]. For this reasons, the average thickness of this small measured region is roughly equivalent to the volume.

As shown in Table 2, 2DLACS and 3DLACS show similar clinical validity in case/control analyses, which was also similar to results found when comparing 3DLACS to an independent study [9]. The suitability of 2DLACS as a substitute for 3D LACS is also confirmed by the high degree of correlation (R2 =0.76) between measurements taken using the 2 methods. Bias in the Bland Altman plot was expected since, due to the necessary modifications, we did not expect 2DLACS to measure the same quantity as 3D LACS or to have an exactly linear one-to-one relationship, possibly due in part to susceptibility artefacts. Such bias does not affect the use of either technique in regression models and our results suggest either method could be used.

The responsiveness for 3D LACS was higher than for 2DLACS however the improvement was modest and might be mitigated by potential cost savings. For some trials, where it is crucial to maximize the responsiveness, 2DLACS may not be ideal; a cost-benefit analysis would shed light on this.

We have also demonstrated that a version of the LACS method can be applied to T2 weighted TSE or fast-spin echo (FSE) pulse sequence. This may be useful for studies no 3D sequence is acquired specifically for quantifying cartilage thickness and the method could be retrospectively applied to studies where only 2D sequences of knees with osteoarthritis were acquired.

We found only a very modest loss of responsiveness and discriminate validity when using 6 or 5 slices in place of 7. This implies that the method could be made faster and more convenient to the reader. Quite often the outer and inner most of the 7 slices contain partial volume artifacts that impede segmentation requiring a substantial amount of additional manual corrections by the reader. Using 2DLACS with 5 or 6 slices may be appropriate for studies involving a large number of MRI scans where it is important to minimize reader time.

Our study has several limitations. We have performed the 2DLACS measurement on a single TSE pulse sequence developed for OAI; there is no proof that it will perform as well on other 2D protocols. For the most part, our method relies on a slice-by-slice segmentation but a model-based 3D segmentation may perform better.

We performed the analysis on only half of the FNIH cohort. However a sample size of 301 is large and sufficient to demonstrate the method and the 301 chosen subjects were exactly

matched to the full cohort. As with 3D LACS, 2DLACS is currently limited to the femur, however the same principle using mathematically robust coordinate system could be applied to the tibia and patella. This is the subject of ongoing work.

Conclusions

We have documented and validated a novel software technique to provide quantitative measurements of cartilage volume on low-resolution 2D MRI scans. This is a potentially valuable method for past and future studies of knee OA.

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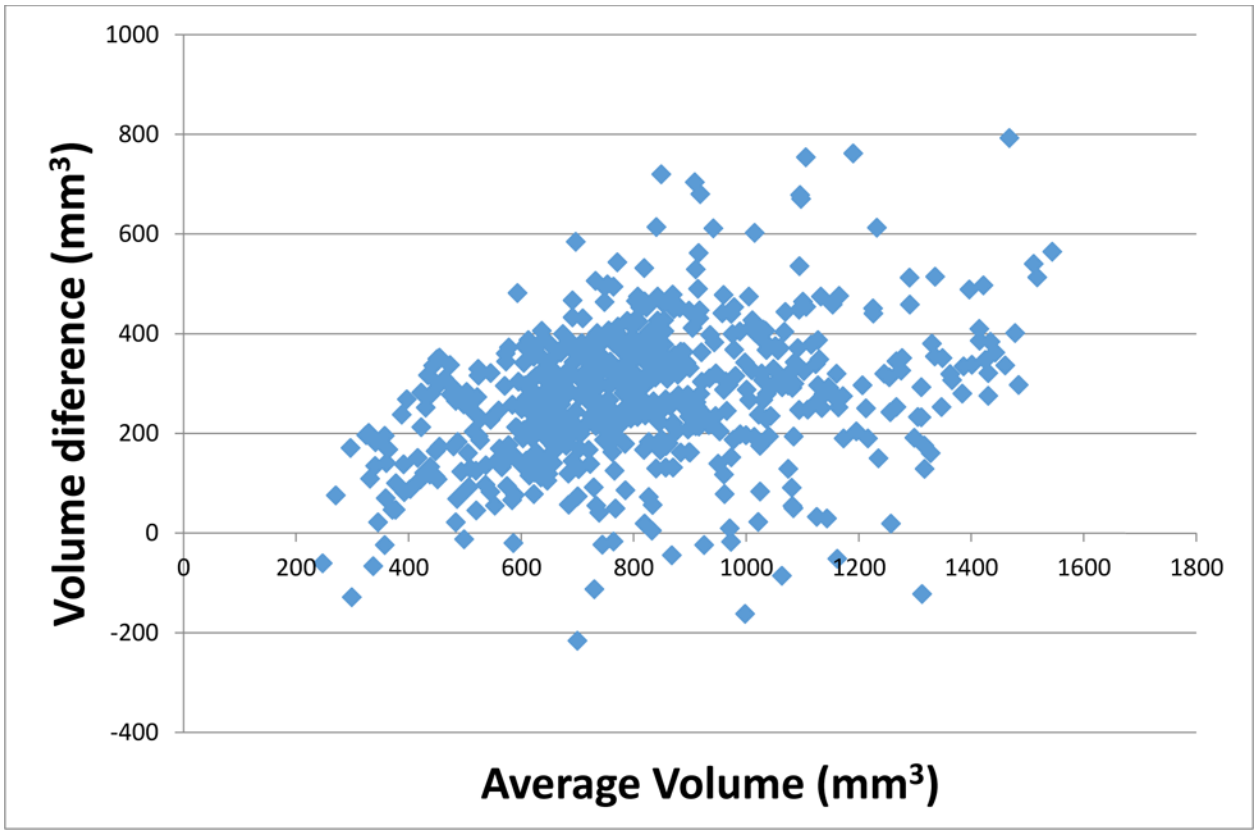

Figure 1.
Bland Altman graph of the difference between 3D and 2D cartilage volume versus the average. As expected, there is an offset and some indication of a bias.

Table 1

Baseline to 24 month change in cartilage volume. For comparison we also include a results from an independent study[9] in the last row of the table. The data were available as part of the public data release of the OAI. These results were from cartilage volume in a central medial weight-bearing region of the medial femur, a location similar but not exactly the same as ours.

	Primary analysis: cases versus controls[1]	Group 1 versus 4 [1]	Group 2 versus 4 [1]	
	Adjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**p-value**
3D DESS	1.62 (1.23–2.13)[2]	3.33 (1.95–5.66)[2]	5.20 (2.43–11.11)[2]	0.000
2D TSE for 7 slices	1.78 (1.34–2.37)[2]	3.11 (1.96–4.94)[2]	2.20 (1.35–3.60)[2]	0.002
2D TSE for 6 slices	1.71 (1.29–2.25)[2]	2.81 (1.81–4,.37)[2]	2.26 (1.38–3.69)[2]	0.001
2D TSE for 5 slices	1.71 (1.30–2.26)[2]	2.77 (1.80–4.26)[2]	2.33 (1.42–3.85)[2]	0.001
Central medial femur[9]	1.77 (1.32–2.60)[2]	4.71 (2.60–8.53)[2]	6.84 (3.03–15.46)[2]	0.000

	Group 3 versus 4 [1]		Group 1,2,3 versus 4 [1]	Groups 1 +2 versus 3 +4 [1]	Groups 1 + 3 versus 2 +4 [1]	
	Adjusted OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**P-value**
3D DESS	1.28 (0.61–2.65)	0.513	2.64 (1.71–4.06)[2]	3.55(2.27–5.55)[2]	1.25(0.97–1.60)	0.088
2D TSE for 7 slices	1.13 (0.68–1.87)	0.639	2.09 (1.49–2.92)[2]	2.53 (1.79–3.58)[2]	1.38 (1.07–1.78)	0.014
2D TSE for 6 slices	1.11 (0.68–1.83)	0.676	2.03 (1.46–2.83)[2]	2.47 (1.76–3.46)[2]	1.32 (1.03–1.70)	0.030
2D TSE for 5 slices	1.07 (0.66–1.75)	0.782	2.02 (1.45–2.81)[2]	2.48 (1.77–3.47)[2]	1.32 (1.03–1.69)	0.031
Central medial femur[9]	1.02 (0.56–1.87)	0.948	2.68 (1.79–4.01)[2]	4.13 (2.65–6.45)[2]	1.25 (0.97–1.63)	0.089

[1] Group 1 consisted of knees with both radiographic and pain progression (primary cases, n=194).

Group 2 consisted of knees with radiographic progression only (n=103).

Group 3 consisted of knees with pain progression only (n=103).

Group 4 consisted of knees with neither radiographic nor pain progression (n=200).

Group 1 was defined as cases in the primary analysis. Group 2, 3 and 4 were combined as controls in the primary analysis.

[2] p-value <0.0001