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Quantitative measurement of medial femoral knee cartilage volume – analysis of the OA Biomarkers Consortium FNIH Study cohort

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SUMMARY

Objective: Large studies of knee osteoarthritis (KOA) require well-characterized efficient methods to assess progression. We previously developed the local-area cartilage segmentation (LACS) software method, to measure cartilage volume on magnetic resonance imaging (MRI) scans. The present study further validates this method in a larger patient cohort and assesses predictive validity in a case–control study.

Method: The OA Biomarkers Consortium FNIH Project, a case–control study of KOA progression nested within the Osteoarthritis Initiative (OAI), includes 600 subjects in four subgroups based on radiographic and pain progression. Our software tool measured change in medial femoral cartilage volume in a central weight-bearing region. Different sized regions of cartilage were assessed to explore their sensitivity to change. The readings were performed on MRI scans at the baseline and 24-month visits. We used standardized response means (SRMs) for responsiveness and logistic regression for predictive validity.

Results: Cartilage volume change was associated strongly with radiographic progression (odds ratios (OR) = 4.66; 95% confidence intervals (CI) = 2.85–7.62). OR were significant but of lesser magnitude for the combined radiographic and pain progression outcome (OR = 1.70; 95% CI = 1.40–2.07). For the full 600 subjects, theSRM was −0.51 for the largest segmented area. Smaller areas of cartilage segmentation were also able to predict the case–control status. The average reader time for the largest area was less than 20 min per scan. Smaller areas could be assessed with less reader time.

Conclusion: We demonstrated that the LACS method is fast, responsive, and associated with radiographic and pain progression, and is appropriate for existing and future large studies of KOA.

Introduction

Osteoarthritis (OA) is a highly prevalent, disabling disease, with tremendous individual and socioeconomic burden that mostly affects elderly people[1]. To date there are no disease modifying treatment options available for OA.

Imaging is important for the diagnosis and assessment of OA both in the clinical setting as well as the research environment. For knee OA, radiography continues to be a primary imaging modality, due to convenience and cost. However, soft tissue such as cartilage cannot be visualized directly in knee radiographs; joint space width provides only an indirect measurement of cartilage. Although more costly and time-consuming than radiography, magnetic resonance imaging (MRI), with its good soft tissue contrast, is the superior option for evaluating some OA-related structures such as cartilage, bone marrow lesions, and the menisci[2].

Objective, reliable, and fast methods to determine knee cartilage volume are needed for large OA trials and observational research. Existing studies of knee OA such as the Osteoarthritis Initiative (OAI)[3,4] and the Multicenter Osteoarthritis Study (MOST)[5] each have tens of thousands of individual knee MRI scans. The vast

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majority of the MRI data from the OAI has not been assessed for quantitative cartilage measures since resources were not provided for this purpose. Additionally, large numbers of MRI data sets will likely be necessary to appropriately power future longitudinal clinical trials of knee OA. Clinical trials for OA therapies also rely on highly responsive measures of structural change so that statistically significant differences in disease progression between the treatment and placebo arms can be found. Quantitative as well as semi-quantitative methods to assess cartilage status in knee OA exist[2]. Semi-quantitative methods[6,7] are based on a qualitative assessment and provide ordinal rather than continuous measurements, and can be cost intensive due to high reading time and the requirement for an experienced reader with specialized training and expertise in musculoskeletal radiology. Quantitative methods were reported to be superior to semi-quantitative methods in assessing cartilage change for knee OA[8,9]. Efforts to decrease MRI reader time, while maintaining performance, directly address the high cost of radiological imaging for current and future studies of knee OA.

We previously developed and validated an efficient, reproducible, and responsive quantitative software tool to measure cartilage volume in focal locations on the medial femur on MRI scans[10,11]. The local-area cartilage segmentation (LACS) method uses anatomical landmarks and a mathematically robust coordinate system to identify consistent regions of cartilage for fast segmentation. The goal of our current study is to further explore the responsiveness and examine clinical validity in a substantially larger cohort by applying LACS to a case–control sample of knee OA progression, and investigate refinements to improve efficiency. We expect to demonstrate that this method is ideal for existing and future large studies of knee OA that use MRI.

Methods

Study design and cohort

For this study, we analyzed subjects that make up the OA Biomarkers Consortium FNIH Study (https://oai.epi-ucsf.org/datarelease/FNIH.asp), a nested case–control study within the OAI. The OAI is a longitudinal cohort study of 4796 men and women ages 45–79 with, or at risk for, knee OA at the beginning of the study. Knee radiography and MRI as well as a clinical assessment were performed annually. In addition, biochemical specimens were collected from all participants. A primary objective of the OAI is to create a public resource for identifying, characterizing, and validating a broad range of imaging biomarkers for OA of the knee that could be used to investigate basic research hypotheses and to serve as outcomes in clinical trials of new therapies[4].

The goal of the OA Biomarkers Consortium FNIH Study is to find structural and biochemical biomarkers for radiographic and pain progression in knees with mild to moderate OA. Details of the design of this study have been published elsewhere[12–14]. Briefly, it includes 600 subjects in four subgroups based on radiographic and pain progression. Radiographic progression was defined by medial tibiofemoral joint space loss $\geq$0.7 mm from baseline to 24, 36, or 48 months measured on conventional radiographs acquired with a fixed-flexion protocol[15]. Pain progression was defined as a persistent increase on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale between 24 and 60 months. Based on this, the cohort was subdivided into four groups:

Group 1: radiographic and pain progressors ($n = 194$).
Group 2: radiographic-only progressors ($n = 103$).
Group 3: pain-only progressors ($n = 103$).
Group 4: no radiographic or pain progressors ($n = 200$).

For the main analysis, we adhere to the case/control definition established by the FNIH researchers[16] having both radiographic and pain progression (Group 1) as cases and combining the other three groups (2, 3, and 4) to be controls. For secondary analyses, and to make a direct comparison with another study[17], 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).

Image analysis and reader procedure

The readings were performed on sagittal double echo steady state (DESS) 3D MRI scans (sagittal, 0.365 mm 0.365 mm, 0.7-mm slice thickness, repetition time 16.5 ms, echo time 4.7 ms) at the baseline and 24-month visits with the reader (LS) blinded to time point and case–control status (see Fig. 1). All knees were evaluated at a fixed measurement location in the central weight-bearing portion of the medial femur as described in a previous publication[10]. Briefly, the measurement region was based on two axes of a cylindrical coordinate system, z and θ. z roughly corresponded to the medial-lateral direction (greater z was more medial) and θ to the anterior-posterior part of the articular surface of the femur (greater θ was more posterior). Since the coordinate system is linked to anatomical landmarks, the effective size (in mm) of the z variable changes with knee size.

Using custom software, the reader used the LACS method to segment cartilage in the regions specified by the coordinate system. The software informed the reader of the slices required to evaluate the cartilage in the required z-range, and the limits on each slice to ensure coverage in θ. Automated image analysis tools were also provided to increase speed and objectivity, including edge detection algorithms that the reader could initiate in areas adjacent to the cartilage margins and a method for the reader to indicate areas of denuded cartilage. The automated steps increased objectivity and minimized the need for manual segmentation by providing tools to allow the reader to guide the automated software when corrections were required.

Reproducibility

The LACS method was previously validated for intra-reader and inter-reader reliability and showed good reproducibility with intraclass correlation coefficients (ICCs) > 0.9)[10]. In a recent published study the repositioning error of the LACS method for $\Delta z = 0.1$ was measured on 10 healthy volunteers with a modified DESS-sequence twice on the same day where the subjects were

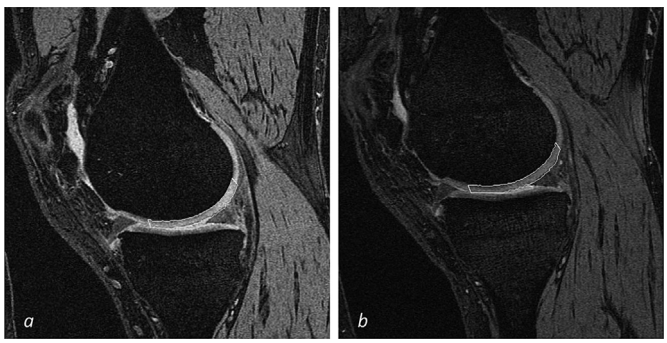

Fig. 1. Corresponding segmented cartilage areas at baseline (a) and follow-up (b).