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SCIENTIFIC ARTICLE

T2 map signal variation predicts symptomatic osteoarthritis progression: data from the Osteoarthritis Initiative

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Abstract
Objective The aim of this work is to use quantitative magnetic resonance imaging (MRI) to identify patients at risk for symptomatic osteoarthritis (OA) progression. We hypothesized that classification of signal variation on T2 maps might predict symptomatic OA progression.
Methods Patients were selected from the Osteoarthritis Initiative (OAI), a prospective cohort. Two groups were identified: a symptomatic OA progression group and a control group. At baseline, both groups were asymptomatic (Western Ontario and McMaster Universities Arthritis [WOMAC] pain score total <10) with no radiographic evidence of OA (Kellgren–Lawrence [KL] score ≤ 1). The OA progression group ($n = 103$) had a change in total WOMAC score greater than 10 by the 3-year follow-up. The control group ($n = 79$) remained asymptomatic, with a change in total WOMAC score less than 10 at the 3-year follow-up. A classifier was designed to predict OA progression in an independent population based on T2 map cartilage signal variation. The classifier was designed using a nearest neighbor classification based on a Gaussian Mixture Model log-likelihood fit of T2 map cartilage voxel intensities.
Results The use of T2 map signal variation to predict symptomatic OA progression in asymptomatic individuals achieved a specificity of 89.3 %, a sensitivity of 77.2 %, and an overall accuracy rate of 84.2 %.
Conclusion T2 map signal variation can predict symptomatic knee OA progression in asymptomatic individuals, serving as a possible early OA imaging biomarker.

Keywords T2 map · Osteoarthritis · MRI · Nearest neighbor classification

Introduction

Radiographs are the imaging gold standard for osteoarthritis (OA) progression, but are unable to detect early OA [1]. Quantitative MRI has the potential to provide sensitive and specific measurements of cartilage injury in the early stages of OA. There have been preliminary applications of compositional MRI techniques to detect changes in water and proteoglycan content and anisotropy of collagen fibers associated with early degradation [2–5].

The MRI transverse relaxation time (T2) is an imaging sequence that holds tremendous potential in detecting early stages of OA before symptomatic or radiographic presentation. The T2 signal is a quantitative parameter dependent on cartilage water content and fiber anisotropy [3, 6–8]. Early in the pathogenesis of OA, changes in cartilage anisotropy and water content produce less variability in T2 values between neighboring voxels. These changes result in less signal variation between voxels in the T2 map, leading to increased homogeneity. This is in contrast to the normal articular cartilage, where regional variations in collagen fiber anisotropy and

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water content provide a well-recognized pattern of signal variation [3, 9, 10].

Multiple groups have postulated that changes in signal variation can be used as an imaging biomarker for OA. Previous reports have demonstrated differences in signal texture metrics between control and OA groups [11] and in a single population as arthritis progressed [12]. T2 signal texture metrics created from multiple image features can be used as an imaging biomarker to predict OA progression in asymptomatic groups [10]. No single imaging measurement of knee cartilage voxels has been prognostic of symptomatic OA progression.

We postulate that disruption of the normal spatial variation in the cartilage T2 signal might be used as an early OA imaging biomarker. To test this hypothesis, T2 map cartilage signal variation between two asymptomatic groups, where one group had symptomatic OA progression and the other group did not progress, was quantified and compared. Patients were collected from a prospective cohort, the Osteoarthritis Initiative (OAI).

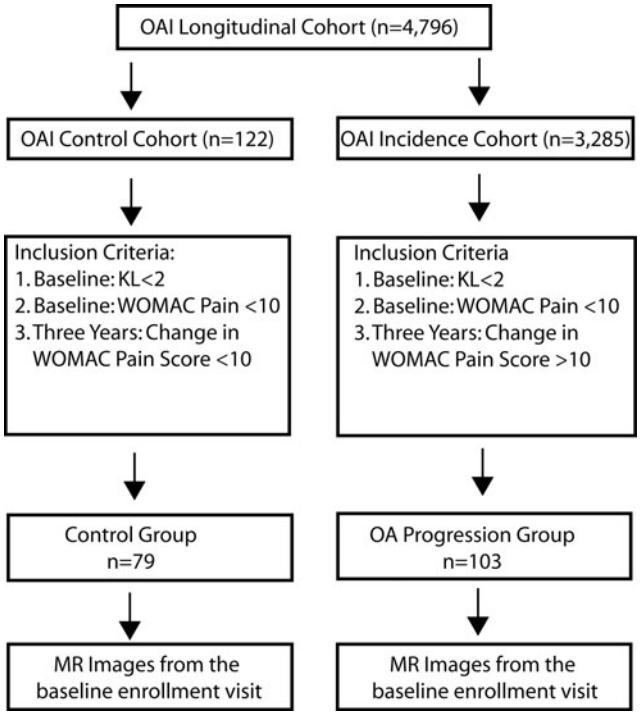

Fig. 1 Experiment design schematic [10]. The Osteoarthritis Initiative (OAI) control cohort was used to build the nonprogression group ($n = 79$). The OAI incidence cohort was used to build the rapid progression population ($n = 103$). At the initial time point, both populations were asymptomatic. At the 3-year time point, the rapid progression population experienced a Western Ontario and McMaster Universities Arthritis (WOMAC) score change > 10. T2 map signal variation was quantified using Gaussian mixture models (GMMs) applied to the baseline images. A classifier, a stochastic variant of the nearest neighbor classification, designed based on the training data sub-set, was used to predict OA progression on an independent test set, with the test set classification accuracy then measured

Materials and methods

Study design and population cohort

To determine if T2 map signal variation could predict OA progression we used a matched prospective study from the Osteoarthritis Initiative (OAI). The OAI is a large prospective cohort ($n = 4,796$) following participants for more than 8 years that have or are at an increased risk for developing OA. The OAI ($N = 4,796$) is divided into a series of three sub-cohorts, the normal control unexposed reference sub-cohort ($n = 122$), the incidence sub-cohort ($n = 3,285$), and the progression sub-cohort ($n = 1,389$). Annual radiography, MRI, and clinical assessments are performed. A primary objective of the OAI is to create a public repository of images that can be used to identify imaging biomarkers for OA. The OAI is a public–private partnership between the National Institutes of Health and the pharmaceutical industry, and is managed primarily by the University of California, San Francisco, USA [13].

For this study, two groups were identified, a control and a progression group. A total of 182 patients were selected from the OAI. Control subjects were selected from the OAI control sub-cohort. The group was defined at baseline and at 3 years by a Western Ontario and McMaster Universities Arthritis (WOMAC) pain score <10 with a Kellgren–Lawrence (KL) score ≤2. The progression group was selected from the OAI incidence sub-cohort. The group was defined by the baseline criteria of a WOMAC pain score less than 10, but with a change in the WOMAC pain score of > 10 within 3 years from baseline, and minimal radiographic signs of OA with a KL score ≤2 (Fig. 1). The WOMAC pain score is composed of five questions related to pain with different activities (Supplementary Table 1). The WOMAC pain score was selected as a measure of symptomatic progression, as it has been a well-described and validated patient reported outcome measure. Each group (control and progression) consists of their respective OAI sub-cohort (control, incidence) as identified by the inclusion and exclusion criteria. In the control group, additional patients were excluded because baseline MRI images did not exist or a minority of randomly selected patients were excluded to create the matched cohort study to match age, gender, and BMI between the two study groups. All images used in this study were collected at the initial baseline visit during the enrollment period, unless otherwise noted. All images collected in this study were part of a normal course of participation in the OAI, and no images were collected outside of the OAI study protocol.

Image acquisition, registration, segmentation, and T2 maps

The femoral cartilage on T2 map sequences at baseline needed to be segmented so that signal intensity in each voxel of femoral cartilage could be identified. To accomplish this, DESS images were used for segmentation as there is increased contrast between cartilage and soft-tissue structures. The DESS images then need to be registered to the respective T2 map of each patient so that the segmented mask of femoral cartilage could be applied to the T2 map.

In the OAI cohort, three-dimensional sagittal DESS and T2 mapping images were acquired from the imaging database, which is freely available on request (http://oai.epi-ucsf.org). Three-dimensional DESS with water excitation images and T2 mapping images were acquired using sequences approved for the National Institutes of Health (NIH)-sponsored Osteoarthritis Initiative study at 3 T [13]. MRI of the knee joint was performed on a 3.0-T Siemens whole-body MAGNETOM Trio 3 T scanner (Siemens, Erlangen, Germany) using a standard extremity coil. For high spatial resolution 3D double echo steady-state (DESS) imaging [14], a total of 160 sections were acquired with a field of view (FOV) of 14 cm (matrix 384 × 384) with an in-plane spatial resolution of 0.365 × 0.365 mm, a slice thickness of 0.7 mm, and an acquisition time of 11 min. For a sagittal 2D dual-echo fast spin echo (FSE) sequence for mapping T2 relaxation time, TR was 2,700 ms and 7 echo images with TE ranging 10–80 ms were acquired with matrix of 384 × 384, in-plane resolution of 0.313 × 0.313 mm, FOV of 12 cm, acquisition time 12 min, and slice thickness 3 mm. All participating institutions obtained institutional review board approval, and informed consent was obtained by all participants in the study.

The DESS and T2 images were registered using mattes mutual information metric and segmented using an active shape model, as previously described [10, 15]. Segmentation of the femur was completed on DESS images and binary masks of the lateral and medial femoral condyle and the patella were generated from the segmented images. T2 maps were calculated from the multi-slice–multi-echo T2 images using a linear least squares fitting method [16].

Classifier design and training

An image classifier, a stochastic variant of the nearest neighbor classification, was used to quantify differences in the signal variation and to develop a model to predict OA progression [17]. Voxel signal variation in femoral cartilage was modeled by building Gaussian mixture models (GMMs) using the expectation maximization algorithm [17] and determining the number of components by minimizing the Bayesian information criterion [18]. A separate GMM was built for each training image.

A stochastic variant of the nearest neighbor algorithm was used for the classification of progression and control groups. Analogous to the traditional nearest neighbor algorithm, which finds the training point that is nearest to the current test point, our classification algorithm finds the training image GMM model that, when used to fit to the test image, gives the greatest data log likelihood. We then use the winning model's class label as the prediction of the patient's class. In this way, we predict for the test patient whether or not their condition will develop into symptomatic OA. Specific details of the construction of the GMM, expectation maximization, the Bayesian information criterion, and pruning are included in the Supplementary methods section.

To assess the performance of the classifier, we randomly divided the entire cohort into ten independent, separate, and equal-sized training and test sub-sets, with equal numbers of control and progression individuals. In each of the ten trials, the classifier was trained to discriminate between control and progression OA populations using the training set, and the accuracy of the classifier and confusion matrix were measured on the independent test set. It should be emphasized that the training and test sub-sets were independent, and measurements of the accuracy of the model did not include any images from the training set used to build the model.

Results

Signal variation in the femoral cartilage of T2 maps was quantified. There are multiple ways to measure signal variation between adjacent voxels. Several different voxel arrangements were tested (Fig. 2). We found that the optimal accuracy is obtained by measuring signal variation in a horizontal direction (horizontal bivariate model).

The receiver operating characteristic (ROC) curve illustrates the performance of a binary classifier system (Fig. 3). To create the ROC curve, we first calculated, for each test image, the difference in log-likelihood under the best-fitting OA model and the best-fitting control model. We then sequentially detected test images in decreasing order of this log-likelihood difference. The area below the ROC curve is 0.87. At a selected operating point on the ROC curve, specificity and sensitivity were 89.3 % and 77.2 % respectively, and the overall accuracy was 84.2 %.

Discussion

Given that T2 values can represent the loss of structural organization in cartilage, we hypothesized that variation in

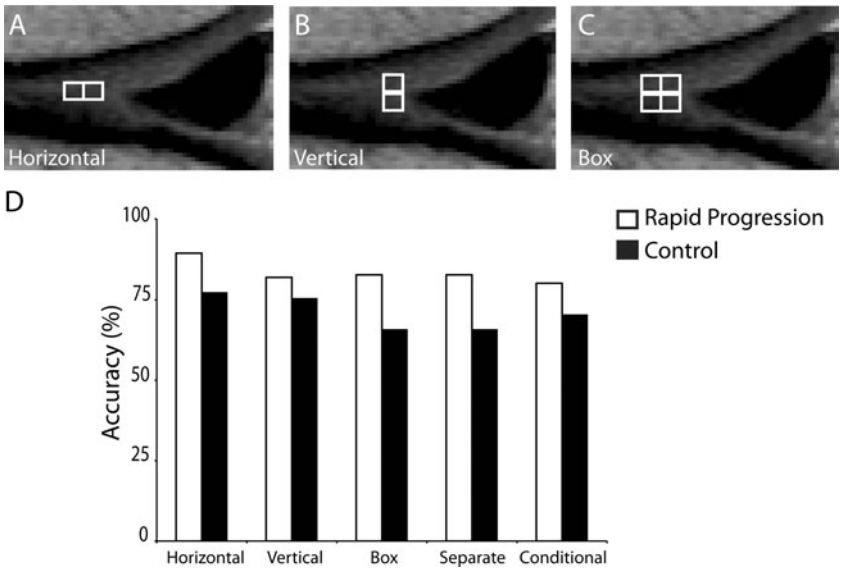

Fig. 2 Classification accuracy for five candidate GMMs. **a** Horizontal bivariate, **b** vertical bivariate, **c** four-pixel box multivariate, univariate, and conditional horizontal bivariate. **d** The horizontal bivariate model gives the best accuracies, both for the control and rapid progression populations

cartilage voxel intensity on T2 maps could be used as an imaging biomarker for the symptomatic progression of OA as measured by the WOMAC score. Signal variation was quantified using a mixture model that could incorporate sub-populations of different voxel intensities, and a classifier was used to separate these groups. Overall accuracy was 84 %.

Multiple methods have been used to quantify T2 map signal variation. Previous work has used different texture metrics to quantify signal variation. These include a histogram, the gray level co-occurrence matrix (GLCM), and the gray level run length matrix. On a longitudinal basis in populations developing OA, the GLCM has been shown to change as a function of time [12]. Comparing controls and populations at an increased risk for developing OA, differences in the mean T2 signal, GLCM contrast, and variance were elevated [19]. Compared with unexposed controls, populations that have clinically significant OA had differences in signal texture [11]. We have reported that texture metrics can be combined into a single value and used as a prognostic imaging biomarker [10].

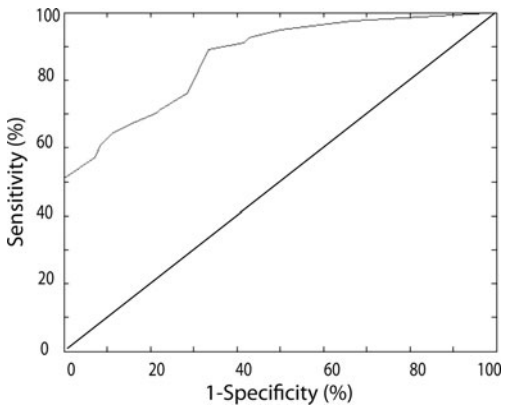

Fig. 3 Receiver operating characteristic (ROC) analysis demonstrates prognostic accuracy. Sensitivity is measured as the true-positive rate. Specificity is one minus the false-positive rate. The *diagonal line* represents the result of random chance

Our results here support these findings, extend these results, and achieve improved discrimination of the OA progression and control groups. Unlike previous work using multiple texture metrics to quantify signal variation, a single measure, cartilage signal variation, could be used to predict OA progression. Mixture models allow the presence of sub-populations of voxel intensities to be represented in an overall population. Compared with different texture metrics where multiple metrics can be selected, we described here signal variation using a single model. A classifier is used to transform the measurements of MR signal variation into an imaging biomarker. We improved on the accuracy of previous models using this technique. It works by comparing a test image with models of trained images and making a decision based on finding the nearest neighbor, i.e. finding the training image that most resembles the test image. These findings support the concept that T2 mapping can monitor cartilage degeneration in OA from an early time point. The overall accuracy of the approach demonstrates the feasibility of using T2 signal variation as an imaging biomarker in early OA. Further work assessing the reproducibility and sensitivity to change across different populations for this potential biomarker, as outlined in the Outcome Measures in Rheumatology (OMERACT) filter, needs to be completed. The ability to differentiate patients at risk for symptomatic OA progression would be valuable in clinical and epidemiological studies for disease-modifying OA drugs (DMOADs) and joint-preserving surgical interventions.

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Compliance with Ethical standards

Author contributions All of the authors were involved in the experimental or software design, data analysis, and manuscript preparation.

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