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RESEARCH ARTICLE

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Predicting osteoarthritis onset and progression with 3D texture analysis of cartilage MRI DESS: 6-Year data from osteoarthritis initiative

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Abstract

In this study, we developed a gray level co-occurrence matrix-based 3D texture analysis method for dual-echo steady-state (DESS) magnetic resonance (MR) images to be used for knee cartilage analysis in osteoarthritis (OA) studies and use it to study changes in articular cartilage between different subpopulations based on their rate of progression into radiographically confirmed OA. In total, 642 series of right knee DESS MR images at 3T were obtained from baseline, 36- and 72-month follow-ups from the OA Initiative database. At baseline, all 214 subjects included in the study had Kellgren-Lawrence (KL) grade <2. Three groups were defined, based on time of progression into radiographic OA (ROA) (KL grades ≥2): control (no progression), fast progressor (ROA at 36 months), and slow progressor (ROA at 72 months) groups. 3D texture analysis was used to extract textural features for femoral and tibial cartilages. All textural features, in both femur and tibia, showed significant longitudinal changes across all groups and tissue layers. Most of the longitudinal changes were observed in progressors, but significant changes were observed also in controls. Differences between groups were mostly seen at baseline and 72 months. The method is sensitive to cartilage changes before and after ROA. It was able to detect longitudinal changes in controls and progressors and to distinguish cartilage alterations due to OA and aging. Moreover, it was able to distinguish controls and different progressor groups before any radiographic signs of OA and during OA. Thus, texture analysis could be used as a marker for the onset and progression of OA.

KEYWORDS
cartilage, DESS, magnetic resonance imaging (MRI), osteoarthritis (OA), texture analysis

Ari Väärälä and Victor Casula contributed equally to this manuscript.

1 | INTRODUCTION

Magnetic resonance imaging (MRI) is an optimal modality for non-invasive evaluation of articular cartilage thickness, integrity, and quality in osteoarthritis (OA) studies, because of its superior soft-tissue contrast, and multiplanar capability.[1] Compared to radiographic detection of joint space narrowing, MRI is more sensitive to cartilage loss.[2] Earlier studies have shown that quantitative MRI (qMRI), like T2 and T1ρ mapping, can be used to detect changes within the cartilage extracellular matrix.[3,4]

Gray level co-occurrence Matrix (GLCM) based texture analysis provides a way to extract textural features from an image. These features are statistical measures of the arrangement of pixel intensities in a region and provide information on spatial heterogeneity,[5] which tends to increase in biological tissue as structural disorganization caused by an underlying pathology progresses. Although originally designed for analyzing aerial photographs,[5,6] this image processing method has been taken into use in the field of medical image processing.[7–21] Texture analysis studies have been applied in 2D, i.e., separately on single slices, using quantitative T2 and T1ρ maps and those have shown that the method can detect signs of OA in cartilage.[10,21,22] Furthermore, texture analysis studies applied on brain T1 and T2 weighted images, and knee dual-echo steady-state (DESS) images, have shown the potential in analyzing non-quantitative images.[23,24] Texture analysis can provide information about localized variations in cartilage collagen matrix, thus providing the ability to differentiate healthy subjects from subjects at risk for OA progression.[13,17] In earlier 3D texture analysis studies,[19] GLCMs were constructed across multiple slices (the third dimension) using the original 3D volumetric data without transformations and rotations of the pixel coordinates. However, this approach has limited directions for neighboring pixels, and it is not possible to follow the geometry of the cartilage and its laminar structure. Neither 2D nor 3D texture analysis approach has been employed for cartilage laminar analysis. Hence, in this study we propose a new method developed to perform more complex textural analyses of the cartilage in 3D. The new method extracts textural features for three different subsets of cartilage layers and the full thickness cartilage.

The 3D DESS is a combination of T1 and T2 weighted images, where the signals from two consecutive echoes, the FID-signal of a FISP sequence (fast imaging steady precession) and the echo-signal of a PSIF (reversed FISP), are separately acquired and the combined. The PSIF part of the sequence provides a high T2 contrast, and the FISP part provides representative morphological images with T1/T2 ratio dominated contrast.[25] All in all, DESS provides images with high contrast between cartilage and fluids, it has the advantage to combine morphological and quantitative analysis of cartilage from the same dataset with high resolution, and the imaging time is relatively short.[25–28] The possibility of isotropic resolution of DESS and the optimal contrast for cartilage suit well for automated segmentation.[29] Previously, the GLCM-based 3D texture analysis method has not been applied to clinical MRI images of articular cartilage, and only one study used the method on MRI of joints to assess vertebral trabecular bones using sagittal T1-weighted MR images.[30] For 3D texture analysis, isotropic coverage creates less distortion in coordinate transformations and rotations. Compared to qMRI methods, the DESS sequence is available for most clinical MRI scanners and sites, and it allows complete coverage of knee cartilage typically in less than 6 min. Thus, the 3D texture analysis method can be applied directly to DESS images without the need for mono-exponential fitting like in the case of T1ρ and T2.

There are currently no established imaging biomarkers able to diagnose OA at an early stage and predict its progression rate, which can vary considerably between patients.[31] Generally, the radiological progression of OA is slow and can take several years or even decades.[32–38] However, it has been reported that in some cases, progress can be rapid and within 12 months, subjects with normal knee radiographs can develop radiographic OA (ROA),[39] or incident OA subjects can progress to advanced-stage ROA.[40]

The purpose of this study was to develop a 3D texture analysis method to be used for knee cartilage analysis in OA studies and clinical trials. Currently, there are no validated methods to predict the development of ROA from morphological images or any imaging markers. OA progresses at different rates and the longitudinal clinical Osteoarthritis Initiative (OAI) dataset enables us to study this, by creating different groups based on their time of progression into ROA. Earlier, 2D texture analysis for qMRI has shown promising results in finding differences between regions of interest (ROI) of healthy and degenerated cartilage before radiographic signs of OA. We hypothesize that 3D texture analysis of DESS images, given their higher resolution and 3D nature, would be even more sensitive to early cartilage changes and it could be used to predict the development of OA before any radiographic signs.

2 | MATERIALS AND METHODS

2.1 | Study population

The proposed method was applied on a selected subset from a longitudinal cohort study, the OAI, enrolling 4796 subjects in total (https://nda.nih.gov/oai/study-details).[41] The OAI database is divided into three cohorts: a Progression cohort consisting of symptomatic knee OA patients with definite tibial-femoral osteophyte (OARSI grades 1–3) at baseline and pain, aching or stiffness on most days of a month in the past year; an Incidence cohort including subjects with frequent knee symptoms without ROA but with two or more other eligibility risk factors; and a Control cohort with no symptoms, no ROA in either knee at baseline and no risk factors.

A total of 214 subjects were selected for our study from the OAI participants aged 65 years or younger with Kellgren-Lawrence[42] (KL) grade <2 at baseline and DESS MR images of the right knee available at baseline (00m), 36-month (36m), and 72-month (72m) follow-ups (Figure 1). They were classified in three groups based on the time of progression into ROA (KL ≥2). The control group ($N = 65$) included subjects selected from the OAI Control cohort with KL grade <2 at all time points ($N = 65$). Subjects in the slow progressor group were selected from the OAI Incidence and Progression cohorts diagnosed with ROA only at 72m ($N = 71$). Subjects in the fast progressor group

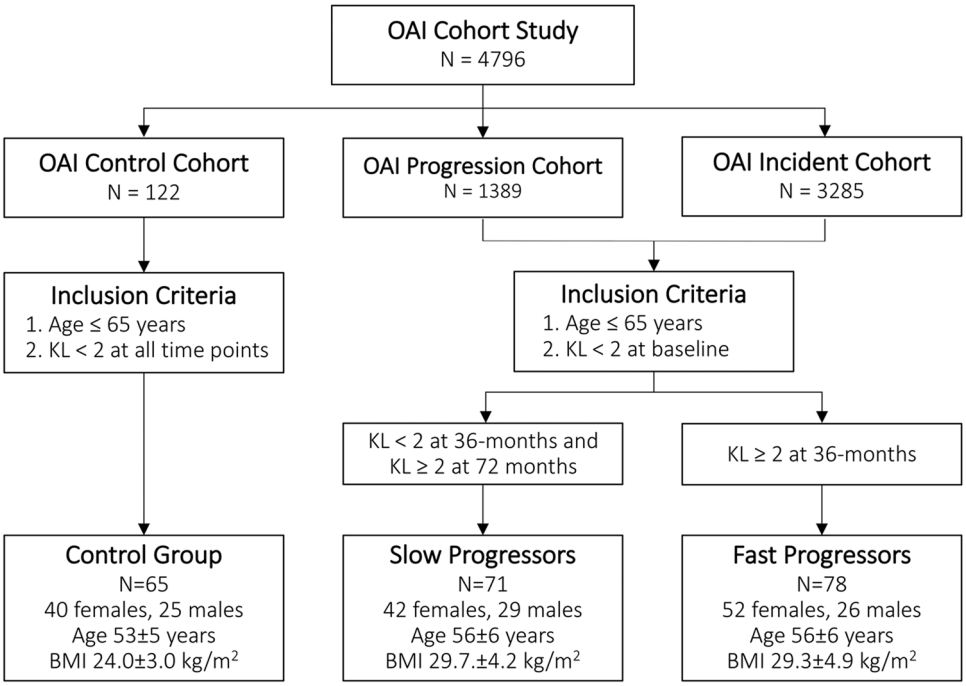

FIGURE 1 Flow chart of the subgroups selection based on the time of progression into radiologic osteoarthritis (Kellgren-Lawrence ≥2), from the cohorts of the Osteoarthritis Initiative database for controls, fast progressors, and slow progressors

were selected from OAI Incidence and Progression cohorts diagnosed with ROA already at 36m ($N = 78$).

2.2 | MRI acquisition and data preprocessing

MR images were acquired using 3T Siemens clinical MR systems (Siemens Healthcare) according to the OAI knee MRI protocol.[41] In total, 642 DESS images of right knees were segmented using the automatic deep learning-based method that was previously trained and validated against manual segmentations.[43] As an output, the software produced separate segmentation masks for femoral, tibial, and patellar cartilage tissues, as well as menisci. Subsequently, the full cartilage masks were automatically segmented into the MOAKS-based compartments via elastic registration to a multiatlas of 10 scan-segmentation pairs.[44] For 3D texture analysis, full cartilage segmentations, and central medial and lateral compartments for femur and tibia are used. The average local thickness of cartilage was measured for the aforementioned compartments.[45] The mean thickness of full femoral and tibial cartilage tissues was determined from the compartmental measurements. Thickness data was used as a reference, to assess whether the textural feature changes were following the changes in the cartilage thickness.

2.3 | 3D texture analysis

The proposed method for 3D texture analysis of cartilage DESS images was developed in-house using Matlab (MathWorks Inc.). The software extracts textural features from a 3-dimensional area defined by the DESS MR image and the segmentation mask. After anatomical normalization, the GLCM matrices for each configured direction are generated from neighboring pixels, which are layered on a plane parallel to the bone-cartilage interface (BCI). These GLCMs are summed for the full cartilage thickness data (SUM). Additionally, the 1-pixel thick layers, at 10% (L10), 50% (L50), and 90% (L90) of relative cartilage thickness from the BCI (Figure 2), have their own a GLCMs. Thickness in this context should not be confused with the average local cartilage thickness, because anatomical normalization requires interpolation and extrapolation of scattered data to grid-aligned data, where pixel coordinates are rounded up to pixel level. More details about anatomical normalization and GLCM populating are provided in the Supporting Information B document.

For this study, 19 textural features[5–7] were extracted from the full femoral and tibial cartilages and the central medial and lateral compartments using our novel 3D texture analysis. Textural features were extracted for four different layers: for three one-pixel thick 3D layers, L10, L50, and L90 (Figure 2), and 3D full cartilage thickness (SUM). Pixel intensities were divided into eight linear analysis bins using a gray level range of 0–300, where pixel intensities greater than 300 are placed in the eighth bin. Pixel offset value was set to 1, and the number of analysis directions (angles) to 8 (0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315°).

2.4 | Statistics

Statistical analysis was performed using Matlab. Differences between groups at the same time points were analyzed using the

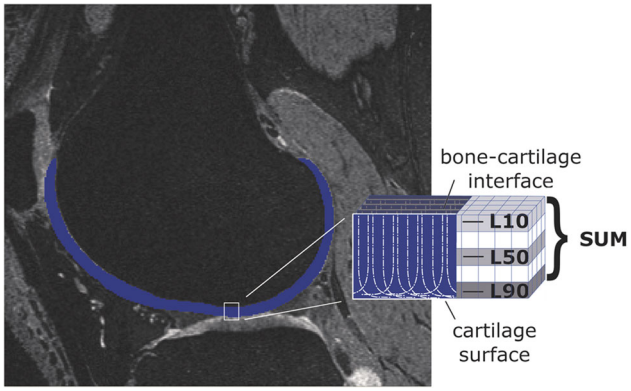

FIGURE 2 Sagittal view of 3D DESS MR image slice with femoral cartilage in blue. The textural features are extracted from one-pixel thick 3D layers L10, L50, and L90. The SUM contains textural features from all cartilage data. The positions of the layers, thickness wise, are illustrated in the zoomed part of the cartilage, which is also showing collagen orientation. DESS, dual-echo steady-state; MR, magnetic resonance

Kruskal–Wallis test and longitudinal changes within the groups using Friedman's test. All *p* values were adjusted with Bonferroni correction for multiple comparisons for both textural features and thickness. The Bonferroni correction was used in triplets for each textural feature: at each time point and in each layer for the group comparisons, and in each layer within each group for the longitudinal comparisons. In addition, the Benjamini-Hochberg method with a 10% false discovery rate was applied to textural feature *p* values of each group comparison, in each time point in each layer, and *p* values of the longitudinal comparisons between each time point in each layer. The correlation between body mass index (BMI) and texture features was assessed using Spearman's correlation.

3 | RESULTS

3.1 | Full cartilage textural features

All textural features, from femoral and tibial cartilage, showed significant longitudinal changes across all groups and layers. Most, but not all, longitudinal changes were observed in progressor groups. Several features, like **contrast** (Figure 3) and **entropy** (Figure 4), increased over time, in both cartilages; on the other hand, features like **energy** (Figure 5) and **homogeneity** (Figure 6) decreased over time. Other features such as **correlation** (Figure 7), did not show a monotonic trend and showed less longitudinal changes. In a number of features, including **contrast**, **energy**, **entropy**, and **homogeneity**, the larger differences between time points were found in the tibia. Differences between groups were seen mostly at baseline and 72 months.

At baseline, significant differences between controls and progressor groups were found in several textural features and layers. Most of the differences were found between controls and slow progressors in the femur L90, while differences between controls and fast progressors were found often in the tibia L10. **Correlation**, **cluster prominence**, **information measure of correlation 2**, **sum of squares**, and **sum variance**, showed significant differences between controls and both progressors in all layers in femur and tibia. In several features, most differences occurred either in the femur (**energy**, **entropy**, **sum entropy**, **maximum probability**, and **autocorrelation**) or in the tibia (**contrast**, **cluster shade**, **difference variance**). Other features differed between controls and either fast or slow progressors in different tissues and layers. For example, **difference entropy**, **dissimilarity**, **homogeneity**, **inverse difference**, and **sum average** had significances between controls and slow progressors, but not between controls and fast progressors. On the other hand, **cluster shade** in the femur had significances between controls and fast progressors but not between controls and slow progressors. Finally, **information measure of correlation 1** had significances between controls and slow progressors only in the femur (all layers) but between controls and fast progressors in the tibia (all layers); while **entropy** and **sum of entropy** in the tibia differentiated controls from fast progressors in L10 and controls from slow progressors in L90. At 36 months, almost all the significant differences were observed between fast progressors and controls, mostly in the femur in L10 and L50. The only feature showing differences at 36 months, between controls and slow progressors, occurring only in the tibia (all layers except L90), was **information measure of correlation 1**. At 72 months, significant differences between controls and progressors were found for all textural features and most of the layers, with the majority of the significances seen between controls and fast progressors. Finally, significant differences between slow and fast progressors were observed only at 72 months in the tibia SUM. Descriptions of full cartilage results per textural feature, medians, interquartile ranges, and group comparison *p* values of each textural feature for all groups, layers, and time points are presented in the Supporting Information C document (Tables SC1–SC6).

3.2 | Textural features of central medial and central lateral compartments

All textural features, from femoral and tibial cartilage, showed significant longitudinal changes across all groups, layers, and compartments. Most of the significant longitudinal changes were observed in progressor groups. The control group showed significant longitudinal changes mostly between baseline and 36 months. On the other hand, both progressors showed significant changes also between 36 and 72 months, the majority of them observed in the fast group. Textural features for the SUM behaved similarly as in full cartilage data: for example, **contrast** and **entropy** statistically significantly increased over time, **energy** and **homogeneity** statistically significantly decreased, and c**orrelation** showed less longitudinal significant changes compared to other features. The majority of the longitudinal significant changes in the control group in the tibia were found on the lateral side, otherwise significant longitudinal changes were spread more evenly between lateral and medial compartments.

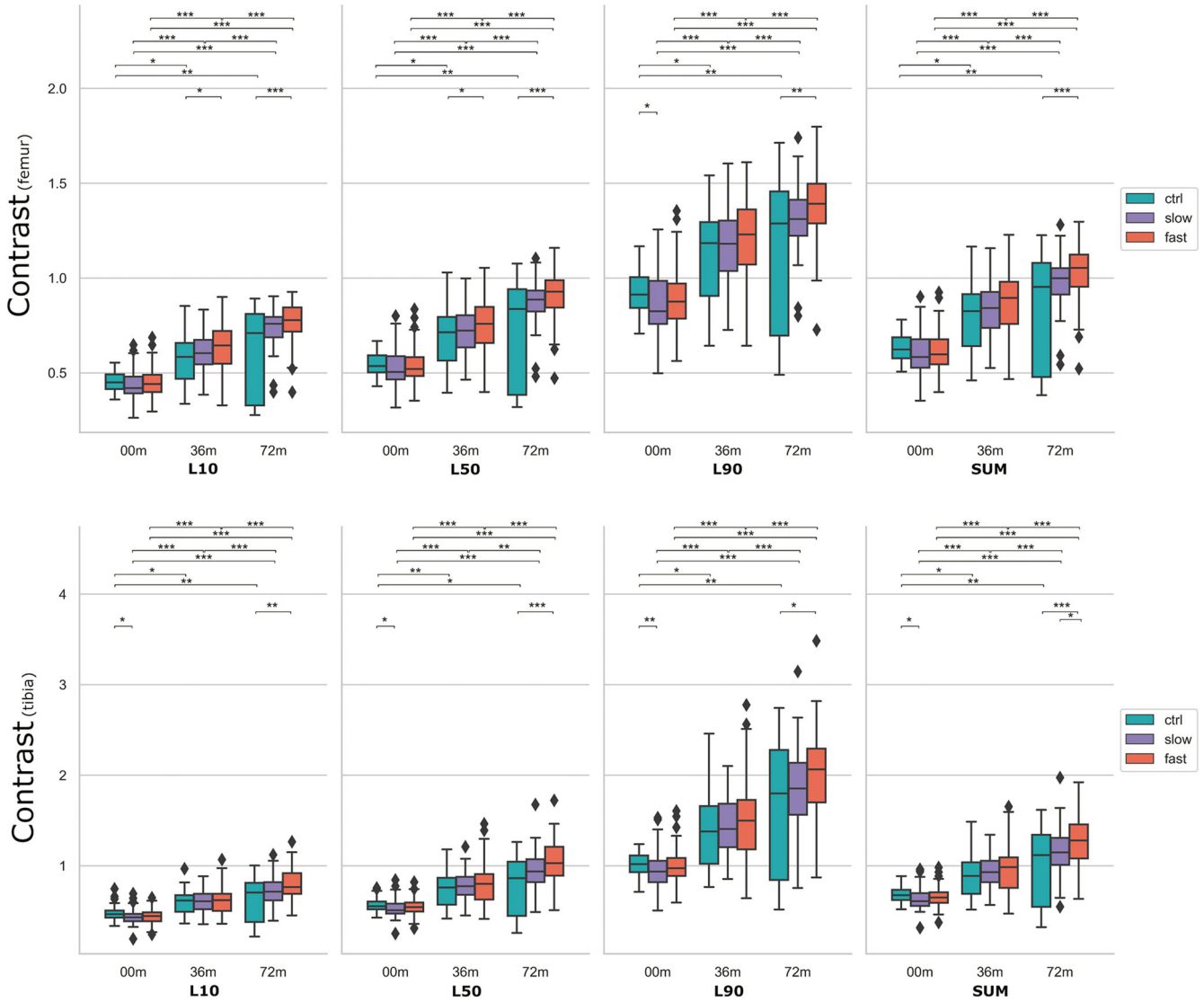

FIGURE 3 Full cartilage femoral and tibial box plots of textural feature contrast for controls (ctrl), slow progressors, and fast progressors at baseline (00m), 36-month (36m), and 72-month (72m) follow-ups. L10, L50, and L90 indicate results of one-pixel thick 3D layers at 10%, 50%, and 90% of relative cartilage thickness from the bone-cartilage interface. The SUM contains results from full cartilage thickness. Horizontal lines inside the boxplots indicate median values, boxplot edges indicate interquartile range, whiskers indicate 1.5 times the interquartile range, and diamonds indicate the outliers (***$p < 0.001$, **$p < 0.01$, *$p < 0.05$)

All the baseline significances in the femur were observed between controls and slow progressors, and the majority of them on the lateral side. However, most baseline significances in the tibia, like **cluster prominence**, **cluster shade**, **correlation**, **information measure of correlation 1** and **2**, **sum of squares**, and **sum variance**, were observed between controls and fast progressors, on the medial side. At 36 months textural features like **contrast**, **difference entropy**, **dissimilarity**, **entropy**, **homogeneity**, and **inverse difference** showed significances between controls and both progressors in the lateral tibia. At 72 months, most of the significant differences in the femur were observed on the medial side, but in the tibia, most of the significances were on the lateral side. Finally, at 72 months, the majority of textural features showed significances between controls and progressors, but only **energy**, **entropy**, **maximum probability**, **sum entropy**, **sum of squares**, and **sum variance** showed significances between slow and fast progressor in the tibia on the central lateral compartment. Descriptions of compartmental SUM results per textural feature, medians, interquartile ranges, and group comparison *p* values of each textural feature for all groups, layers, and time points are presented in the Supplemental C document (Tables SC7–SC18).

3.3 | Textural features versus BMI and cartilage thickness

Correlation coefficients between texture features and BMI were mostly nonsignificant or very weak-to-weak. Cartilage thickness, conversely to texture analysis, was significantly different at baseline

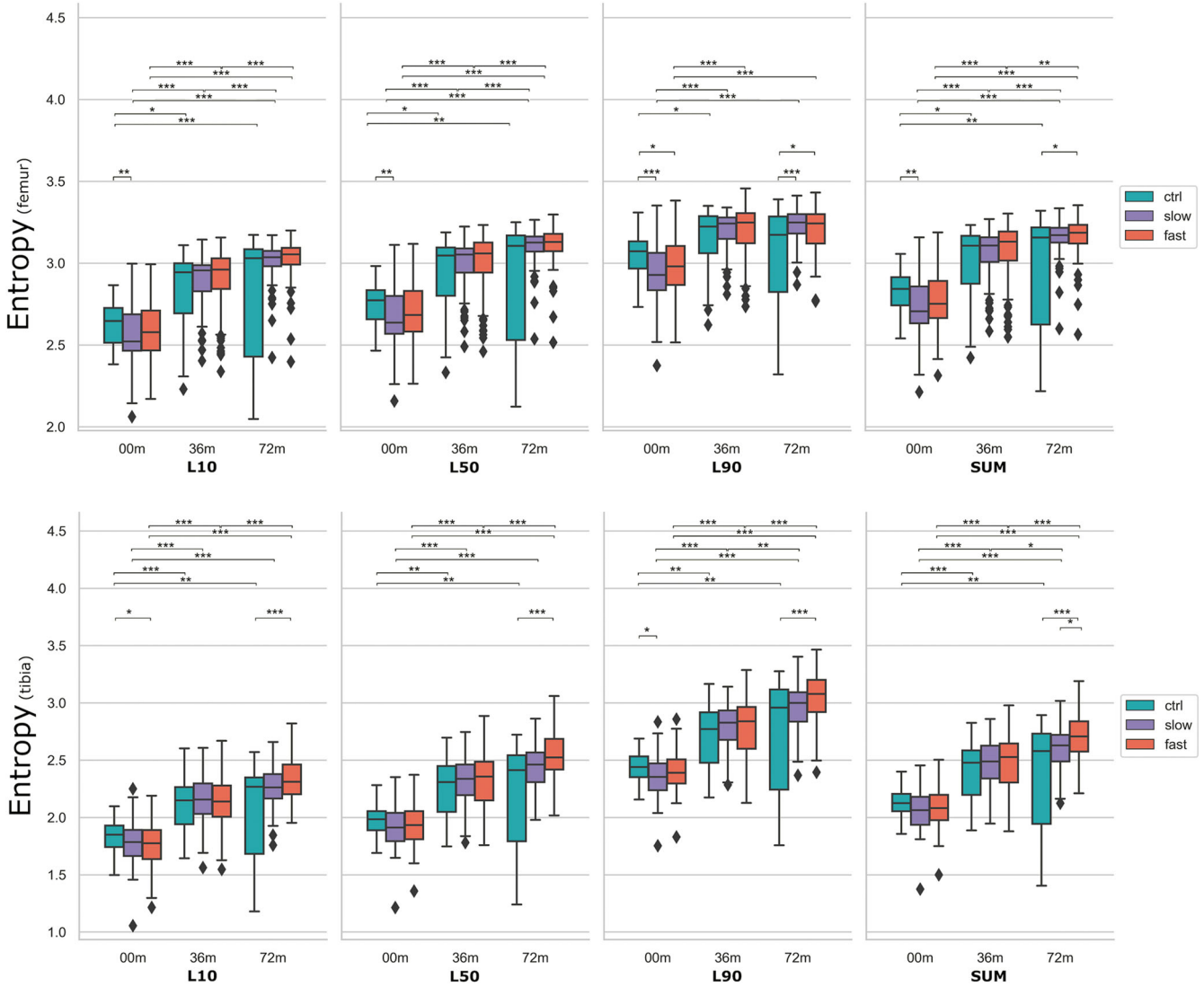

FIGURE 4 Femoral and tibial box plots of textural feature entropy for controls (ctrl), slow progressors, and fast progressors at baseline (00m), 36-month (36m), and 72-month (72m) follow-ups. L10, L50, and L90 indicate results of one-pixel thick 3D layers at 10%, 50%, and 90% of relative cartilage thickness from the bone-cartilage interface. The SUM contains results from full cartilage thickness. Horizontal lines inside the boxplots indicate median values, boxplot edges indicate interquartile range, whiskers indicate 1.5 times the interquartile range, and diamonds indicate the outliers (***$p < 0.001$, **$p < 0.01$, *$p < 0.05$)

only between controls and slow progressors in femur. Significant differences in cartilage thickness between fast progressors and ctrl were observed only at 36 months in femur. For cartilage thickness results and transversal and longitudinal p-values, see the Supplemental A document (Tables SA1 and SA2, Figures SA1–SA3).

4 | DISCUSSION

In the present study, we compared 3D textural features of 3D DESS MR images between a control group and two progressor groups with different rates of progression into ROA. The fast progressor group developed ROA within 3 years, while the slow progressor group developed ROA between three and 6 years. Nineteen textural features were extracted from full cartilage, and medial and lateral central compartments, in the femur and tibia. Textural features were extracted from four different layers. Three of them are one-pixel thick 3D layers at a certain depth of cartilage thickness (L10, L50, and L90) and one is the 3D full cartilage thickness (SUM). 3D texture analysis was able to detect longitudinal changes in both progressor groups, but also in controls, suggesting worsening of cartilage health due to OA or aging, in all layers. The earliest changes from baseline were observed already at 36 months in all the three groups and in all layers in both femur and tibia and no particular layer seemed to be more frequently affected than other. Differences between controls and progressors were slightly more frequent in femur than in tibia. At baseline, several textural features showed significant differences between control and progressor groups, enabling the possibility of

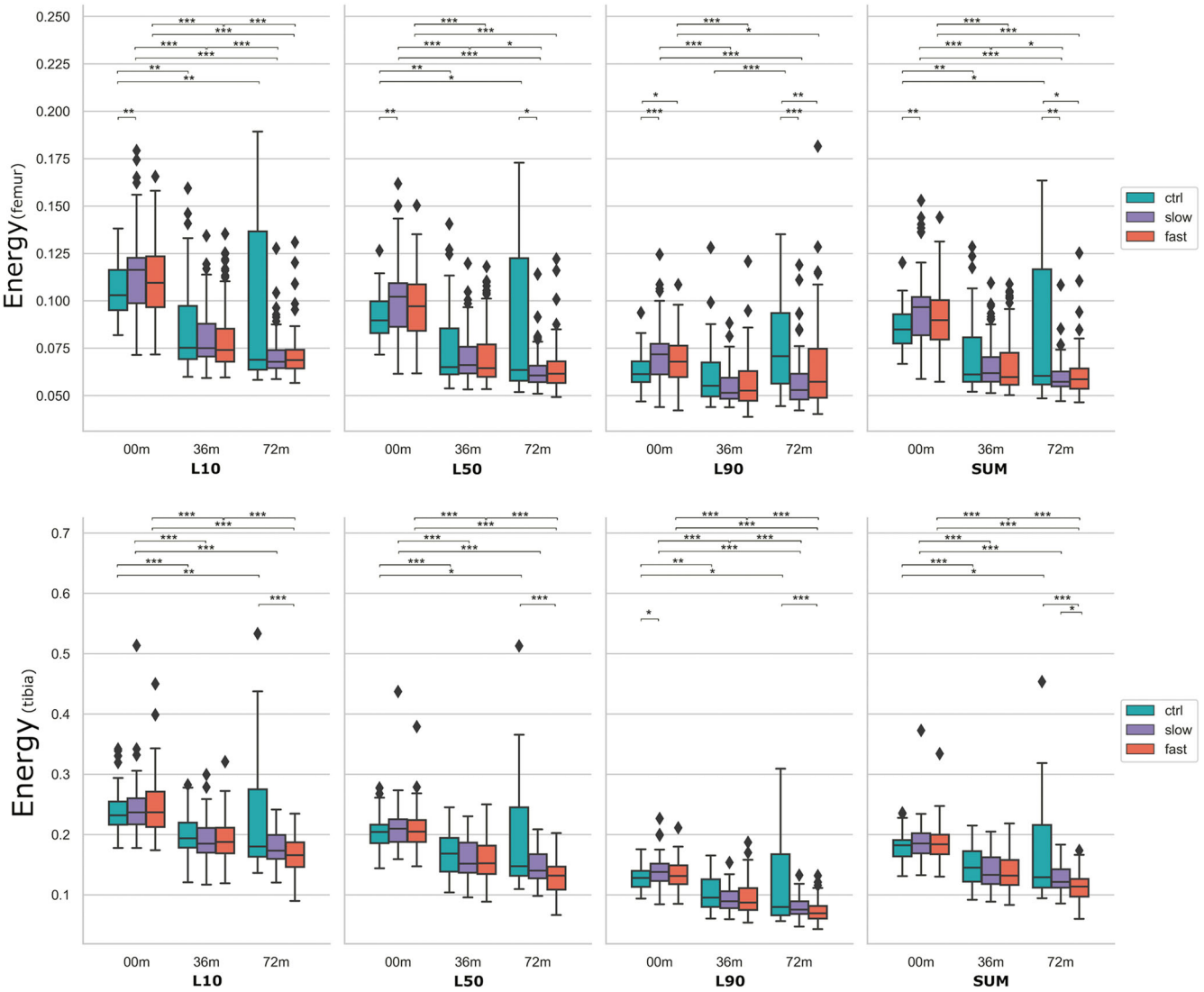

FIGURE 5 Femoral and tibial box plots of textural feature energy for controls (ctrl), slow progressors, and fast progressors at baseline (00m), 36-month (36m), and 72-month (72m) follow-ups. L10, L50, and L90 indicate results of one-pixel thick 3D layers at 10%, 50%, and 90% of relative cartilage thickness from the bone-cartilage interface. The SUM contains results from full cartilage thickness. Horizontal lines inside the boxplots indicate median values, boxplot edges indicate interquartile range, whiskers indicate 1.5 times the interquartile range, and diamonds indicate the outliers (***$p < 0.001$, **$p < 0.01$, *$p < 0.05$)

early diagnosis and prediction of OA development. Compared to controls, early changes at baseline in both progressor groups were seen in all layers. Those changes were most frequently found in superficial femur in slow progressors, which is consistent with the current understanding that early OA changes often start in the most superficial layer of cartilage.[46,47] In fast progressors, changes were also most frequently seen in superficial femur as well as in deep tibia, which might be indicating a possible role of changes occurring in deep layer of tibial cartilage in accelerating the OA onset. Changes in textural features did not follow changes in cartilage thickness, which suggests that cartilage thickness is not a confounding factor. Extracting textural features from femoral and tibial central lateral and central medial compartments did not increase the sensitivity of 3D texture analysis and resulted in a reduced number of significant differences compared to full cartilage analysis. Findings from later time points at 36 and 72 months indicate that 3D texture analysis has the potential to monitor cartilage changes associated with OA onset and progression.

Overall, the current study supports several findings from earlier 2D texture analysis studies using qMRI T2 and T1ρ. However, a comparison of our findings to earlier studies, which were using only one or two slices of knee cartilage, is not so straightforward. In the case of a 2D slice, the number of pixels is in hundreds, and in our case of full femoral cartilage, we are on a scale of over one hundred thousand pixels. Besides the differences in the number of pixels, many of the earlier 2D studies are not following the curvature of the cartilage, which means the texture analysis direction is not on a plane parallel, as in our case, or perpendicular to the bone cartilage

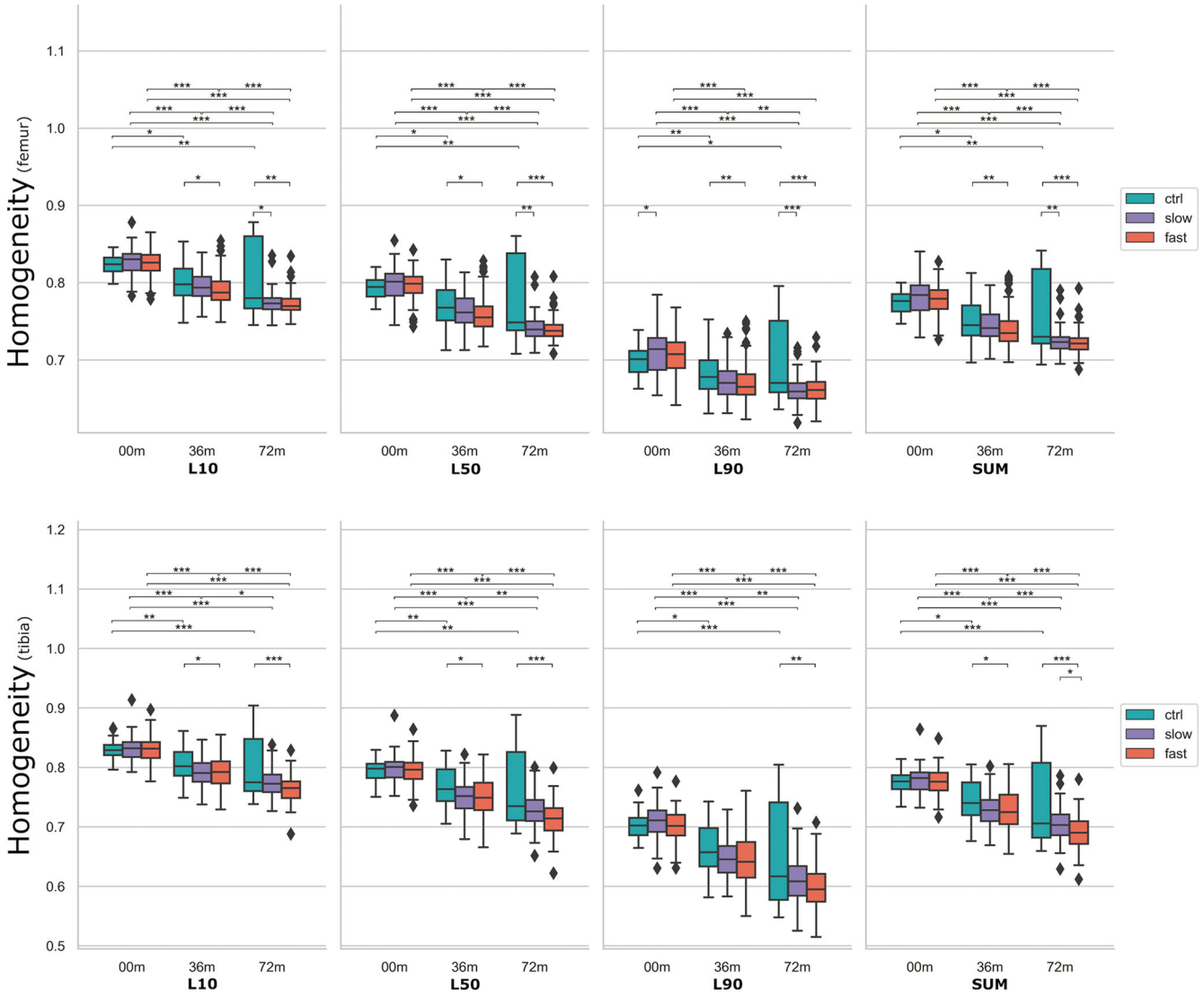

FIGURE 6 Femoral and tibial box plots of textural feature homogeneity for controls (ctrl), slow progressors, and fast progressors at baseline (00m), 36-month (36m), and 72-month (72m) follow-ups. L10, L50, and L90 indicate results of one-pixel thick 3D layers at 10%, 50%, and 90% of relative cartilage thickness from the bone-cartilage interface. The SUM contains results from full cartilage thickness. Horizontal lines inside the boxplots indicate median values, boxplot edges indicate interquartile range, whiskers indicate 1.5 times the interquartile range, and diamonds indicate the outliers (***$p < 0.001$, **$p < 0.01$, *$p < 0.05$)

interface. Offsets and the number of analyzing directions also vary. With 3D DESS MR images, there is also a significant difference in image contrast, compared to T2 and T1ρ.

Blumenkrantz et al.[10] reported a decrease in energy and an increase in entropy of cartilage T2 and T1ρ for OA patients. Our analysis of DESS images shows similarity only at a 72 months time point in L90 in the femur, where both progressors are significantly different from control. At 72 months in the tibia, energy and entropy in SUM can distinguish slow and fast groups, but L90 shows significance only between control and fast. Longitudinally, but only in a 9-month time frame, Blumenkrantz et al.[10] reported that entropy of cartilage T2 significantly decreased in OA patients, but controls showed no significant changes in energy or entropy. However, we found out that over time, energy values are decreasing, and entropy values are increasing, in both progressor and control groups. We observed the biggest longitudinal changes between energy and entropy in the femur in the control group in L90, where entropy has significant change only between baseline and 36 months, and energy has significant change only between 36 and 72 months.

Joseph et al.[13] used subjects from OAI incidence and control cohorts to extract textural features of T2, at baseline. In the incidence group, entropy, contrast, and variance were increased differentiating it from control. In our study textural features can differentiate controls from progressors, especially variance (sum of squares) has strong significances between control and both progressors at baseline. The least amount of significance at baseline can be seen in the contrast in the femur.

Baum et al.[16] conducted a longitudinal study, using baseline and 36 months time points from OAI data. They reported a normal

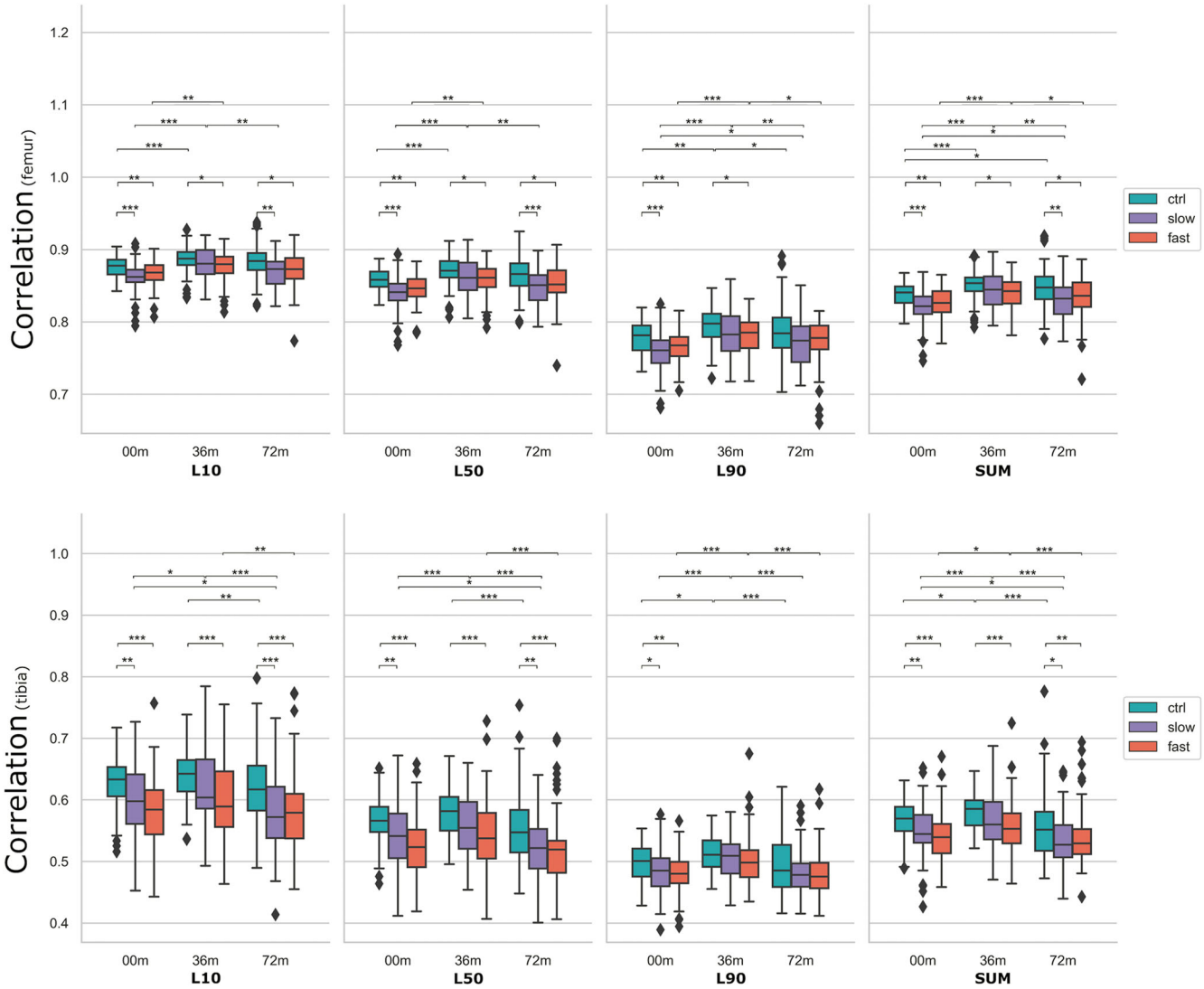

FIGURE 7 Femoral and tibial box plots of textural feature correlation for controls (ctrl), slow progressors, and fast progressors at baseline (00m), 36-month (36m), and 72-month (72m) follow-ups. L10, L50, and L90 indicate results of one-pixel thick 3D layers at 10%, 50%, and 90% of relative cartilage thickness from the bone-cartilage interface. The SUM contains results from full cartilage thickness. Horizontal lines inside the boxplots indicate median values, boxplot edges indicate interquartile range, whiskers indicate 1.5 times the interquartile range, and diamonds indicate the outliers (***$p < 0.001$, **$p < 0.01$, *$p < 0.05$)

control group and subjects with OA risk factors stratified into three groups based on BMI. At baseline, subjects with risk factors for OA had no ROA (KL grade <2). Baum et al.[16] reported constantly elevated T2 entropy in overweight and obese subjects over 36 months. In their study on average over all compartments, entropy is showing a significant difference between control and two highest BMI value groups at 36 months, but not at baseline. Our results, at baseline, are showing significant differences between control and progressors in both femoral and tibial layers. However, at later time points, there are no significant differences until 72 months. Over time, Baum et al.[16] reported an increase in contrast and variance and a decrease in entropy. Our longitudinal findings agree with the contrast and variance findings of Baum et al.[16] but do not agree with the entropy, which is increasing over time.

Kretzschmar et al.[48] investigated compositional changes of knee cartilage at the site of newly appearing cartilage lesions and the surrounding cartilage. Their method requires a specific ROI in a specific slice, to be able to detect the difference. They used the longitudinal OAI data and reported that local cartilage ROIs had higher T2-values compared to the surrounding cartilage, 4 years before lesion onset. They also reported of the 57 new cartilage lesions studied, most occurred in the medial femoral condyle (30%), and the lateral tibia (25%). Even though our study is not focused on finding lesions, similarities between the distribution of significances between medial and lateral compartments can be seen. In our textural features, at 72 months in the femur, the majority of significances were found in the central medial compartment. However, at 72 months in the tibia, the majority of the significances, and only

significances between slow and fast progressors, were observed on the central lateral compartment.

Peuna et al.[21] studied compartmental two-dimensional T2 textural features of symptomatic and asymptomatic subjects. Their method follows the cartilage surface and executes textural analysis parallel to the BCI. They reported significant differences between groups in femoral and tibial cartilage in medial and lateral central compartments. Our findings, in contrast, correlation, energy, entropy, homogeneity, and variance agree with results from Peuna et al.[21] in terms of the direction of change of parameter values in progressor groups.

Carballido-Gamio et al.[11] reported that the subdivision of lateral and medial femoral compartments into weight-bearing and nonweight-bearing regions did not improve discrimination between healthy controls and subjects with mild OA, in two-dimensional textural features of T2 and T1ρ. Our findings agree with this. In both, femur and tibia, when we compare significances between full cartilage data and medial and lateral compartments, it can be observed that full cartilage data provides more significances between groups at baseline. This could suggest that early cartilage changes, seen by texture analysis, might not be solely on weight-bearing compartments of the cartilage.

The current study has several limitations. First, the studied groups were not BMI matched, but on the other hand, BMI did not show a strong correlation with textural features between groups. Second, different knee radiofrequency coils were used during the OAI study. Most of the data used in this study was acquired with similar quadrature transmit-receive coils (same brand and design), which provided comparable signal-to-noise ratio. However, part of the knee MRIs of the control group at 72-month follow-up visit were performed using an eight-channel phased-array coil, with higher performance in terms of signal-to-noise ratio compared to the other coils. This might explain, at least in part, the large variance of the textural features observed in the control group at the last time point. After excluding those subjects from the analysis, significant differences were still observed between control and progressor groups, although the results changed for individual textural features at 72 months, see the Supporting Information D document (Figures SD1–SD7). Third, analysis parameters of texture analysis (e.g., gray-level range, number of bins, and quantization method) can affect the results and need to be thoroughly optimized in the future for optimal sensitivity and robustness. Also, a dataset acquired at isotropic resolution would be preferred for less distorted coordinate transformations.

In conclusion, our novel method is sensitive to early and late cartilage degenerative changes in knee articular cartilage. It was able to distinguish controls and different progressor groups before, and after, any radiographic signs of OA. Moreover, 3D texture analysis of DESS images was able to detect longitudinal changes in controls and progressors, so it is sensitive and capable of distinguishing cartilage changes due to OA and aging. Thus, it could be used as a possible marker for predicting OA onset and progression in clinical trials of new disease-modifying OA drugs. The method does not have any special hardware requirements, it works with a standard MR morphological sequence that can be run on any clinical MRI scanner and does not require acquisition of a separate quantitative image dataset. Therefore, it can be implemented as an adjunct methodology to any ongoing clinical trial in OA.

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CONFLICT OF INTERESTS

Ali Mobasheri is Senior Advisor to the World Health Organization Collaborating Center for Public Health Aspects of Musculoskeletal Health and Aging and “Collaborateur Scientifique de l'Université de Liège” at the Université de Liège in Belgium. He has consulted for Genacol and Sterifarma, companies that produce and market collagen supplements. Ali Mobasheri has also consulted for Sanofi (Brazil), Pfizer Consumer Health, GSK Consumer Health, and Aché (Aché Laboratórios Farmacêuticos), companies that have ongoing R&D activities in joint health supplements. The other authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Ari Väärälä: 3D texture analysis method implementation, data analysis, and manuscript drafting. **Victor Casula**: Design of the study, interpretation of the results, supervising, and manuscript editing. **Arttu Peuna**: 3D texture analysis idea and method implementation support. **Egor Panfilov**: Cartilage segmentations using the automated DL segmentation tool, thickness calculations, and manuscript editing. **Ali Mobasheri**: interpretation of the results and manuscript editing. **Marianne Haapea**: Statistics support and manuscript editing. **Eveliina Lammentausta**: 3D texture analysis idea and method implementation support. **Miika T. Nieminen**: Design of the study, interpretation of results, supervising, and manuscript editing.

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SUPPORTING INFORMATION

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