Title

Extracting Voxel-Based Cartilage Relaxometry Features in Hip Osteoarthritis Subjects Using Principal Component Analysis

Journal

Journal of Magnetic Resonance Imaging, 51(6)

ISSN

1053-1807

Authors

Liao, Tzu-Chieh
Pedoia, Valentina
Neumann, Jan
et al.

Publication Date

2020-06-01

DOI

10.1002/jmri.26955

Peer reviewed

HHS Public Access

Author manuscript

J Magn Reson Imaging. Author manuscript; available in PMC 2022 December 12.

Published in final edited form as:

J Magn Reson Imaging. 2020 June ; 51(6): 1708–1719. doi:10.1002/jmri.26955.

Extracting Voxel-Based Cartilage Relaxometry Features in Hip Osteoarthritis Subjects using Principal Component Analysis

Tzu-Chieh Liao, PT, PhD[1], **Valentina Pedoia, PhD**[1], **Jan Neumann, MD**[1], **Thomas M. Link, MD, PhD**[1], **Richard B. Souza, PT, PhD**[1,2], **Sharmila Majumdar, PhD**[1]

[1]Musculoskeletal Quantitative Imaging Research, Department of Radiology and Biomedical Imaging, University of California-San Francisco, San Francisco, CA, USA

[2]Department of Physical Therapy and Rehabilitation Science, University of California-San Francisco, San Francisco, CA, USA

Abstract

BACKGROUND.—Magnetic resonance (MR) imaging based relaxation time measurements provide quantitative assessement of cartilage biochemistry. Identifying distinctive relaxometry features in hip osteoarthritis (OA) might provide important information on regional disease variability.

PURPOSE.—First, to incorporate fully automatic voxel-based relaxometry (VBR) with principal component analysis (PCA) to extract distinctive relaxometry features in subjects with radiographic hip OA and non-diseased controls. Second, to use the identified features to further distinguish subjects with cartilage compositional abnormalities.

STUDY TYPE.—Cross-sectional.

SUBJECTS.—Thirty-three subjects with radiographic hip OA (sex, 20 males; age, 50.2 ± 13.3 years) and 55 controls participated (28 males; 41.3 ± 12.0 years).

SEQUENCE.—3.0T scanner using 3D SPGR, combined $T_{1\rho}$/T_2, and fast spin echo sequences.

ASSESSMENT.—Pelvic radiographs, patients' self-reported symptoms, physical function, and cartilage morphology were analyzed. Cartilage relaxation times were quantified using traditional regions of interest and VBR approaches. PCA was performed on VBR data to identify distinctive relaxometry features, and were subsequently used to identify a subgroup of subjects from the controls that exhibited compositional abnormalities.

STATISTICAL TESTS.—Chi-square and independent *t* tests were used to compare group characteristics. Logistic regression models were used to identify the possible principal components (PCs) that were able to predict OA *vs.* control classification.

RESULTS.—In $T_{1\rho}$ assessment, OA subjects demonstrated higher $T_{1\rho}$ values in the posterior hip region and deep cartilage layer when compared to controls ($p=0.012$ and 0.001, respectively). In T_2 assessment, OA subjects exhibited higher T_2 values in the posterior hip region ($p<0.001$).

Correspondence Address: Tzu-Chieh Liao, 185 Berry Street, Lobby 6, Suite 350, San Francisco, CA 94710, USA, Tel: 415-476-1000, Fax: 415-353-9423, tzu-chieh.liao@ucsf.edu.

Based on the PC score classification, 16 subjects without radiographic evidence of OA demonstrated relaxometry patterns similar to OA subjects, and exhibited worse physical function (p=0.003) and cartilage lesions (p=0.009~0.032) when compared to remaining controls.

CONCLUSION.—The study identified distinctive cartilage relaxometry features that were able to discriminate subjects with and without radiographic hip OA effectively.

Keywords

hip osteoarthritis; magnetic resonance imaging; principal component analysis; $T_{1\rho}$ and T_2; voxel-based relaxometry

Classification:

Bone < Musculoskeletal imaging < Clinical Science; Clinical Science; Musculoskeletal imaging < Clinical Science

INTRODUCTION

Hip osteoarthritis (OA) is a common joint disorder in middle aged and elderly people, with significant impact on functioning, disability, and health care utilization (1,2). It has been reported that 2.5 million total hip replacements are performed each year in the United States, with most of them for treatment of hip OA (3). Often clinically OA is a late-stage condition where disease-modifying opportunities are limited, as OA typically develops over decades. Defining and characterizing OA in its earlier stage might enable a better understanding of the natural history of OA, as well as the development and examination of disease-modifying treatments.

Magnetic resonance (MR) imaging is often used to study symptomatic, painful hips (4,5), largely because of its ability to visually detect morphological changes in soft tissues such as the labrum and cartilage. In addition, advanced MR sequences can provide a quantitative assessment of tissue biochemistry. For instance, articular cartilage $T_{1\rho}$ and T_2 relaxation times are imaging biomarkers that are sensitive to the compositional changes in cartilage associated with early OA (6,7). T_2 relaxation is directly correlated with water content and associated with the collagen network organization and structure, while $T_{1\rho}$ relaxation is inversely associated with the proteoglycan content of the matrix (8-10). Increased $T_{1\rho}$ and T_2 relaxation times have been found in individuals with radiographic hip OA, specifically in the acetabular cartilage, as compared to healthy individuals (11). Furthermore, abnormal $T_{1\rho}$ and T_2 relaxation times are predictive of hip OA progression as increased $T_{1\rho}$ and T_2 at baseline were found to be associated with worsening of patients' symptoms (12) and MR-defined cartilage lesions (13) at 18-month follow-up.

While large number of studies have examined cartilage relaxometry features in OA, most studies were limited to analyzing average values in specific compartments through regions of interest (ROI) that are mostly arbitrarily designated. More recently, voxel-based relaxometry (VBR) technique has been introduced, which allows voxel-by-voxel comparison across different time points and subjects (12-15). VBR provides the benefit of fully

visualizing the distribution of relaxometry values as it is not confined by the a-priori division of subregions. This increases the sensitivity to detect local differences and distinguish features that may otherwise be masked by the traditional ROI approach. Additionally, VBR adopts an automatic, atlas-based segmentation which removes user bias, variability, and significantly reduces the amount of time for manual segmentation. Our group has successfully demonstrated that VBR is feasible and more sensitive than traditional ROI-based analysis in the hip joint (12,13).

In the VBR analysis each subject's data are registered to a single atlas template, and can be considered as a vector in the feature space. Statistical approaches, such as principal component analysis (PCA), can help to reduce the data dimensionality and extract clinically relevant features (16,17). PCA reduces data by geometrically projecting data onto lower dimensions called principal components (PCs), where each PC, in our case, describes a specific cartilage relaxometry feature. Since the PCs are geometrically orthogonal, each PC is uncorrelated with the others. PCA has been extensively adopted in medical imaging, more commonly in MR neuroimaging (18-20). More specifically, PCA has been used to identify cartilage relaxometry features within the knee cartilage in persons with knee OA and anterior cruciate ligament reconstruction (21). The study demonstrated that PCA effectively revealed relaxometry features that were distinct among the persons with knee OA, with anterior cruciate ligament reconstruction, and healthy individuals. Nevertheless, the application of VBR coupling with PCA in the hip joint is unknown.

As such, the current study proposes to incorporate VBR and PCA to extract distinctive cartilage relaxometry features in hip OA subjects compared to non-diseased controls, and to compare these features against the traditional ROI approach. To accomplish this purpose, PCA was performed on the VBR maps in subjects with and without radiographic hip OA. Our second aim was to provide a classification method based on the identified relaxometry features to further distinguish a subgroup of control subjects with compositional abnormalities by considering PC scores as possible classifiers.

MATERIALS AND METHODS

Subjects

Subjects were recruited from a longitudinal natural history cohort on hip OA. Data included in this study were the baseline time point of this longitudinal study. Subjects were recruited from the community using flyers and advertisements. A screening pelvic radiograph was performed to determine the eligibility. Of 102 subjects originally enrolled, 3 had previous hip surgeries and 1 unknown case. Data were unavailable for 4 subjects and motion artifacts were identified in 6 subjects. These 14 subjects were excluded from the study. In total, 88 subjects were included in this study (Figure 1).

Subjects were excluded if any of the following criteria were present: 1) contraindications to MR imaging, 2) severe radiographic hip OA (Kellgren-Lawrence [KL] grade of 4) (22,23), 3) previous hip trauma, 4) joint replacement of any lower extremity joint, 5) pain or existing OA at any other lower extremity joint, 6) self-reported inflammatory arthritis, and 7) any conditions that limited the ability to walk. Prior to testing, all subjects provided written

informed consent in this study approved by the Committee of Human Research at the University of California, San Francisco.

Radiographic Imaging

To determine radiographic signs of hip OA, an anteroposterior weight-bearing pelvic radiograph was obtained as a screening assessment. All radiographs were assessed using the KL grading system by a board-certified musculoskeletal radiologist with 25 years of experience (TML), where 0 is normal, 1 shows doubtful signs of OA, 2 is mild OA, 3 is moderate OA, and 4 is severe OA (22,23). Study subjects with KL grades of 2 or 3 were classified as radiographic hip OA whereas subjects with KL grades of 0 or 1 were classified as non-diseased controls.

Patient-Reported Symptoms

All subjects completed the self-administered Hip disability and Osteoarthritis Outcome Score (HOOS) (24). The HOOS questionnaire consists of five subscales: pain, symptoms, function in daily living, function in sport and recreation, and hip related quality of life. A normalized score (100 indicating no symptoms and 0 indicating severe symptoms) was calculated for each subscale. HOOS was not utilized for primary statistical analysis, but to provide a basis of patients' self-reported symptoms.

Physical Function Assessment

Physical function was tested using the Timed Up and Go (TUG) test and six-minute walk test (6MWT). In the TUG test, subjects were required to rise from a chair, walk 3 m, turn and come back to sit down. Subjects were instructed to walk as quickly as they could while feeling safe and comfortable. During the 6MWT, subjects were instructed to walk as long a distance as possible during a 6-minute period. Both tests have been shown to be reliable and feasible in persons with hip OA (25-27).

MR Imaging Assessment

All imaging was performed using a 3.0T GE MR 750w scanner (General Electric, Milwaukee, WI, USA) with an 8-channel flexible coil (GE Healthcare, Waukesha, WI, USA). For all scans, the subjects' feet were internally rotated and their forefeet were taped together to achieve a reproducible hip joint position. The hip side with the higher KL grade was scanned whereas for subjects with equal KL grades for both hips, the side was selected at random.

The MR protocol for clinical grading of the hip articular cartilage included intermediate-weighted, fat-suppressed, fast spin echo sequences in the sagittal, oblique coronal, and oblique axial plane with a repetition time of 2400 to 3700 ms, echo time of 60 ms, field of view of 14 to 20 cm, matrix size of 288 x 224 pixels, and slice thickness of 3 to 4 mm. A 3D SPGR (MERGE) sequence was acquired for cartilage segmentation. The MERGE sequence consisted of repetition time of 30.4 ms, 5 echo times (TEs) (effective TE of 12.4 ms), flip angle of 15°, field of view of 14 cm, matrix size of 512 x 512, 28 slices, slice thickness of 4 mm, bandwidth of 62.5 kHz, number of excitations of 1, and an acquisition time of 11:46 min. A combined $T_{1\rho}/T_2$ sequence (11,28) was used to assess hip joint cartilage

proteoglycan content ($T_{1\rho}$) and collagen structure (T_2). The $T_{1\rho}/T_2$ sequence consisted of a field of view of 14 cm, matrix size of 256 x128, bandwidth of 62.5 kHz, recovery time of 1.2 s, views per segment of 64, slice thickness of 4 mm, no-gap, in-plane resolution of 0.5 mm, and an acquisition time of 13:47 min. $T_{1\rho}$ images were obtained using spin lock times (TSLs) of 0/15/30/45 ms (spin lock frequency of 300 Hz), while the T_2 images were obtained using preparation TEs of 0/10.4/20.8/41.7 ms.

Cartilage Lesion Scoring

To assess morphological abnormalities of hip cartilage, an arthroscopically validated, semi-quantitative scoring system (Scoring Hip OA with MR imaging [SHOMRI]) (29,30) was used and lesions were graded by a musculoskeletal radiologist (JN). High intra-reader agreement was previously reported (ICC of 0.92 with a confidence interval from 0.89 to 0.94) (30). The hip joint was divided into 10 anatomical subregions. Four subregions for acetabular cartilage (superolateral, superomedial, anterior, posterior) and 6 subregions for femoral cartilage (lateral, superolateral, superomedial, inferomedial, anterior, posterior) (Figure 2). The 10 subregions were graded separately for cartilage lesions on a three-point scale: 0 (no lesion), 1 (partial thickness cartilage loss), and 2 (full thickness cartilage loss). Total cartilage scores were also graded for acetabular and femoral.

Voxel-Based Relaxometry

Image post-processing was performed with in-house programs written in MATLAB (MathWorks, Natick, MA), integrated with the Elastix registration toolbox for non-rigid image registration (31,32). VBR is based on the registration of all the subjects on a unique space to allow for the comparison of similar anatomic locations on a voxel basis. A single reference subject was preselected through an iterative process aimed to minimize the global image deformation. Due to morphological differences across subjects, a non-rigid registration procedure was adopted to accomplish this task (Elastic registration toolbox). The details of the process have been previously described (12,14). The non-rigid registration technique was applied between the reference and each of the 1st TSL=0, $T_{1\rho}$-weighted image. The transformation field obtained was then applied on all the later TSL images.

$T_{1\rho}$ maps were then computed voxel-by-voxel basis by fitting the morphed images from different TSLs, employing Levenberg-Marquardt mono-exponentials applied to each voxel. T_2 maps were obtained with an identical process on TEs. Example of VBR computation for $T_{1\rho}$ is as follows, where S is the image signal at a given time point, A is initial magnetization, and B is a constant.

$$S(TSL) \propto A\left[exp\left(-\frac{TSL}{T_{1\rho}}\right)\right] + B$$

The reference ROIs were then applied on the morphed maps, setting in this way a fully automatic, single atlas-based segmentation. Relaxation times were also computed using the traditional ROI approach. That is, the average of all voxels within femoral and acetabular

cartilages were quantified respectively allowing for comparison between the classical ROI-based analysis and VBR analysis incorporating with PCA.

To remove the spatial heterogeneity and any differences related to factors such as age, MR system or protocol, $T_{1\rho}$ and T_2 values at each voxel were converted in Z-scores. Average and standard deviation (SD) of the relaxometry values from 7 "supercontrols" were used as reference (mean ± SD; sex, 3 males; age, 34.8 ± 4.7 years; BMI, 23.9 ± 2.5 kg/m^2). The "supercontrols" were selected from the cohort who demonstrated no definite sign of radiographic OA and no MR-defined cartilage lesions (SHOMRI) in the hip joint at baseline, as well as no reported progressions in symptoms (HOOS) and SHOMRI at 36-month follow-up. Example of Z-score computation for $T_{1\rho}$ was as follows:

$$Z(x,y,z) = \frac{T_{1\rho}(x,y,z) - T_{1\rho}Mean_{supercontrol}(x,y,z)}{T_{1\rho}SD_{supercontrol}(x,y,z)}$$

Principal Component Analysis

After obtaining the Z-scores in $T_{1\rho}$ and T_2 maps, PCA was performed to simplify the complexity of the high-dimensional data into fewer dimensions, while retaining trends and patterns. PCA does so by creating new uncorrelated variables (PCs) while maximizing variance. That is, the first PC accounts for the largest possible variance in the data set, then each new PC is orthogonal (uncorrelated) to all previously calculated PCs and captures a maximum variance under these conditions (16). The details for performing PCA were previously described and evaluated (21,33). The effect of each PC mode on the average Z-score map can be modeled individually, by changing the value of each mode from the mean, to the mean ± 3 mode variance. Clinical interpretation of each mode can then be investigated by observing the relaxometry pattern changes. The process was performed individually on the normalized Z-scores for $T_{1\rho}$ and T_2 maps. The first 5 PCs, that describes majority of the overall variation, were subsequently outlined for their clinical interpretation and considered for further analysis.

Subgroup Analysis

Each PC describing a specific relaxometry feature was further used to test if any of the features were distinctive among the radiographic OA and control groups. Within the control group, the identified features were then used to re-classify subjects if they exhibited cartilage relaxometry patterns similar to OA subjects. That is, to identify a subgroup of subjects that exhibited compositional abnormalities but did not show radiographic OA evidence. First, the centroids of the radiographic OA group and control group were identified based on the PC scores. Subgroup analysis was carried out based on the distances from the centroids: control subjects with PC scores laid closer to the OA centroid would be identified. The subset of subjects with compositional abnormalities but no radiographic sign of OA was our target of interest. This subgroup was tested against the remaining controls (no radiographic and compositional abnormalities) to determine if any differences existed between their characteristics (demographics, self-reported symptoms, physical function, and cartilage morphology).

Statistical Analysis

Chi-square and independent *t* tests were used to compare demographics, HOOS subscales, physical function, and SHOMRI between the radiographic OA and control groups. Logistic regression models were used to identify the possible relaxometry features from the first 5 PCs from each $T_{1\rho}$ and T_2 map that were able to predict the OA *vs.* control classification, with the covariates of sex, age, and BMI. The same logistic regression model was also performed for the $T_{1\rho}$ and T_2 averages within the ROIs. Control subjects were re-classified into those with or without compositional abnormalities based on their relaxometry features. Chi-square and independent *t* tests were again used to compare demographics, HOOS subscales, physical function, and SHOMRI between groups. The alpha value was set at 0.05.

RESULTS

Subject Characteristics

Based on the radiographic OA classification, 33 subjects with mild to moderate hip OA (KL grades of 2 or 3) were included in the OA group (sex, 20 males; age, 50.2 ± 13.3 years), and 55 subjects without or with doubtful OA (KL grades of 0 or 1) were included in the control group (28 males; 41.3 ± 12.0 years). Significant group differences were found for age (p=0.002), all HOOS subscales (p ranges from 0.003~0.014), and SHOMRI grades in various acetabular and femoral regions as well as total scores (p ranges from <0.001~0.600) (Table 1).

Principal Component Analysis

The first 5 PCs from $T_{1\rho}$ maps described 29.7% of the overall variation within the dataset and were considered for further analysis (Figure 3). PC1 alone described 12.5% of the total variability within the dataset. Modeling of PC1 revealed that a lower PC1 corresponded to elevated $T_{1\rho}$ values globally; on the contrary, a higher PC1 corresponded to decreased $T_{1\rho}$ values globally. Modeling of PC2 (5.4%) suggested a regional effect, as a lower PC2 corresponded to higher $T_{1\rho}$ values in the inferoposterior hip region as opposed to central region. Modeling of PC3 (4.5%) suggested a bone effect, as a lower PC3 corresponded to elevated $T_{1\rho}$ values in the acetabular cartilage. Modeling of PC4 (3.8%) suggested a laminar effect, as a lower PC4 corresponded to higher $T_{1\rho}$ values in the deep cartilage layer as opposed to superficial layer. Lastly, modeling of PC5 (3.3%) showed a regional effect, as a lower PC5 corresponded to elevated $T_{1\rho}$ values in the inferoposterior and central hip regions.

The first 5 PCs from T_2 maps described 28.3% of the overall variation (Figure 4). Modeling of PC1 (7.8%) revealed that a lower PC1 corresponded to higher T_2 values in the femoral cartilage as opposed to acetabular cartilage. Modeling of PC2 (7.5%) revealed that a lower PC2 corresponded to elevated T_2 values globally. Modeling of PC3 (5.4%) showed that a lower PC3 corresponded to higher T_2 values in the posterior hip region as opposed to central region. Modeling of PC4 (3.9%) showed that a lower PC4 corresponded to elevated T_2 values in the acetabular cartilage; whereas a higher PC4 corresponded to elevated T_2 values in the deep cartilage layer. Lastly, modeling of PC5 (3.5%) suggested a regional effect, as a lower PC5 corresponded to higher T_2 values in the anterior half of the hip as opposed to posterior half.

Osteoarthritis vs. Control Group Comparison

Logistic regression revealed that PC2 (regional effect, p=0.012) and PC4 (laminar effect, p=0.001) from $T_{1\rho}$ maps as well as PC5 (regional effect, p<0.001) from T_2 maps were significant predictors of the radiographic OA *vs.* control group classification (Table 2), when adjusted for sex, age, and BMI. Post hoc analysis showed that the OA group exhibited lower $T_{1\rho}$-PC2 and -PC4 values as well as higher T_2-PC5 values. That is, subjects with radiographic OA demonstrated features of higher $T_{1\rho}$ values in the posterior hip region, higher $T_{1\rho}$ values in the deep cartilage layer, and again higher T_2 values in the posterior hip region when compared to non-diseased controls. Logistic regression for the $T_{1\rho}$ and T_2 averages within the ROIs revealed that none of the variables was a significant group predictor (Table 3).

Subgroup Analysis

Based on PC score classification, 16 subjects from the control group exhibited similar relaxometry patterns to radiographic OA subjects (Figure 5). When comparing this subgroup of subjects with remaining controls, significant group differences were found for TUG test (p=0.003) and femoral cartilage lesions in the lateral (p=0.009) and inferomedial (p=0.032) regions (Table 4).

DISCUSSION

The primary purpose of this study was to identify the relaxometry features in subjects with radiographic hip OA. Our results revealed that PCA demonstrated strong capacity in reducing voxel-by-voxel relaxometry data. Several relaxometry features were significant predictors of the radiographic OA *vs.* control group classification while the same effect was not seen in the ROI averages, suggesting VBR incorporating PCA was a more effective analysis to explore relaxometry features than the traditional ROI approach. The study further identified subjects in the control group who exhibited relaxometry features similar to OA subjects. These subjects, when compared to the remaining controls, not only demonstrated compositional abnormalities but also worse physical function and cartilage lesions.

From all the PC modes analyzed, the most dominant feature among all subjects was marked by global differences of cartilage relaxation times, followed by other features such as bone effect, laminar effect, and regional effect. The strength of PCA especially lies in the non a-priori relaxometry-related features selection as well as full spatial analysis within the cartilage. The primary PC modes that were retained to predict group classification overall explained on average 29% of the variation in the dataset. This percentage was lower than most variances reported in previous PCA studies (18-21); however, due to the large quantity of voxels and complexity of relaxometry signals, extensive amounts of PC modes were required to reconstruct the variance to 100%. Therefore, we opted to retain only the first 5 PCs from each $T_{1\rho}$ and T_2 map in order to reduce the number of comparisons and investigate the more easily interpretable relaxometry features.

Our results were consistent with the well-known global elevation of cartilage $T_{1\rho}$ and T_2 times in the OA population. More specifically, our results suggested that the elevation was

observed in the posterior and inferoposterior hip regions in the OA group (regional effect). This was confirmed with previous analyses performed in the same cohort (11,13). Using a ROI approach, Wyatt et al. (11) reported that radiographic hip OA subjects had higher $T_{1\rho}$ and T_2 in superoposterior acetabular cartilage region, and $T_{1\rho}$ approached significant difference in the inferoposterior acetabular cartilage. Moreover, Gallo et al. (13) reported higher $T_{1\rho}$ and T_2 in the superoposterior femoral cartilage for subjects who demonstrated worsening of MR-defined cartilage lesions over 18-month follow-up. Taken together, OA-related local differences in cartilage relaxation times have been predominantly found in the posterior hip region, adding to the current knowledge that in addition to higher global average relaxation times, elevation in the posterior hip region could be a key biomarker for OA detection.

Interestingly, OA subjects exhibited higher $T_{1\rho}$ values in the deep cartilage layer when compared to controls (laminar effect). However, it should be noted that $T_{1\rho}$ relaxation times are naturally higher in the superficial layer than the deep layer. Therefore, higher $T_{1\rho}$ values in the deep layer in OA subjects led to a decreased difference between the two layers, suggesting a less emphasized laminar effect. Laminar effect in OA population has first been described in knee studies. In persons with knee OA, a similar pattern was reported (21), and the same pattern was observed when static loading was given at the knee (34). Given that composition and structure of articular cartilage differ between layers, the ability of each layer to dissipate forces differs (35). The superficial layer contains collagen fibers aligned parallel to the articular surface and protects cartilage from shear stresses. The deep layer that is closer to the bone contains the highest proteoglycan content and lowest water concentration, as it is responsible for providing the resistance to compressive forces. Since OA has been associated with increased joint loadings (36,37), it is likely that the greater loads have contributed to substantial relaxation time elevation within the deep layer as observed in the current study, leading to a less emphasized laminar difference. While laminar effect seems to be a promising imaging biomarker associated with OA, higher resolution $T_{1\rho}/T_2$ sequence is warranted to confirm our findings due to the limited MR resolution in current hip imaging.

Due to the low spatial resolution of the $T_{1\rho}/T_2$ sequence compared to the thickness of hip cartilage, it remained a great concern that partial volume artifacts may occur in the relaxometry assessment. To address this concern, a qualitative assessment of the morphed maps was performed and no major alterations, which might potentially cause by registration errors or interpolation issues, were noted. Furthermore, in our previous technical paper (12), it has been shown that no correlation existed between algorithm performance and hip KL grade. That is, automatic segmentation performance was independent of the OA severity or the extent of cartilage loss, supporting its use in healthy and OA populations.

The secondary purpose of this study was to provide a classification method based on the identified relaxometry features to further distinguish subjects with compositional abnormalities. Within the control subjects who did not demonstrate radiographic evidence of hip OA, 16 subjects (29.0%) were found to exhibit relaxometry features similar to OA subjects. When comparing these subjects to remaining controls, they exhibited worse physical function and cartilage lesions. The results suggested that using PCA to

extract distinctive relaxometry features was effective in identifying a subgroup of subjects, whom yet to show radiographic signs of degenerative changes but compositional and morphological abnormalities in the cartilages.

Even though TUG test was not a rigorous measure of physical function, it is a simple clinical test used to assess a person's mobility and requires both static and dynamic balance. Factors and consequences associated with a longer TUG are beyond the scope of our discussion, but the measure provides basic information on how the subgroup may perform differently than controls. Other differences observed between the subgroups were worse cartilage lesions in the lateral and inferomedial regions of the femoral cartilage. Even though the regions did not consistently coincide with where higher cartilage relaxation times were found, it added further evidence that the subgroup exhibited different characteristics than controls.

Despite the promising results reported in the current study, some limitations need to be acknowledged. The study has a relatively small study population and a cross-sectional design; thus, the longitudinal changes in relaxometry patterns among hip OA subjects were not explored. Additionally, it is unknown whether the distinctive relaxometry features predict progression of disease. Future studies with a larger sample size and follow-up period would be needed. When performing VBR, only a portion of the hip cartilage slices were segmented and analyzed. It is possible that other relaxometry features existed in cartilage areas that were not segmented. Furthermore, as the acquired voxels had greater dimensions than the cartilage thickness, the spatial resolution of the $T_{1\rho}/T_2$ sequence was limited in the in-plane direction. Nevertheless, we were able to identify laminar difference as a distinctive feature. Higher resolution is needed to localize the subtle differences and would be highly beneficial for pattern extraction. Lastly, while we only considered the compositional biochemical aspect of cartilage degeneration, it is well known that OA is a multifactorial disease including but not limited to biomechanical, morphological, inflammatory, and functional changes associated with degeneration. A comprehensive study that considers all aspects simultaneously is needed to provide better classification for patients and healthy peers.

In conclusion, this study investigated the most clinically relevant hip OA-related cartilage relaxometry features using PCA and showed promising results in identifying the distinctive cartilage relaxometry features that discriminate hip OA subjects from non-diseased controls. Furthermore, when further using cartilage relaxometry as a classifier, the identified subgroup demonstrated worse physical function and cartilage lesions. Our results could be potentially useful in identifying the imaging biomarkers for the early stratification of persons at risk of developing clinical signs of OA. Further investigation should focus on the longitudinal changes of relaxometry features and whether these features are predictive of the progression of hip OA.

Grant support:

Funding was from NIH-NIAMS P50 AR060752, NIH-NIAMS K24 AR072133, and NIH-NIAMS R01 AR069006.

REFERENCES

1. Verbrugge LM, Patrick DL. Seven chronic conditions: their impact on US adults' activity levels and use of medical services. Am J Public Health 1995;85:173–182. [PubMed: 7856776]
2. Prevalence of disabilities and associated health conditions among adults--United States, 1999. MMWR Morb Mortal Wkly Rep 2001;50:120–125. [PubMed: 11393491]
3. Quintana JM, Arostegui I, Escobar A, Azkarate J, Goenaga JI, Lafuente I. Prevalence of knee and hip osteoarthritis and the appropriateness of joint replacement in an older population. Arch Intern Med 2008;168:1576–1584. [PubMed: 18663171]
4. Roemer FW, Guermazi A, Felson DT, et al. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. Ann Rheum Dis 2011;70:1804. [PubMed: 21791448]
5. Amin S, LaValley MP, Guermazi A, et al. The relationship between cartilage loss on magnetic resonance imaging and radiographic progression in men and women with knee osteoarthritis. Arthritis & Rheumatism 2005;52:3152–3159. [PubMed: 16200595]
6. Sasho T, Katsuragi J, Yamaguchi S, et al. Associations of three-dimensional T1 rho MR mapping and three-dimensional T2 mapping with macroscopic and histologic grading as a biomarker for early articular degeneration of knee cartilage. Clin Rheumatol 2017;36:2109–2119. [PubMed: 28456927]
7. Atkinson HF, Birmingham TB, Moyer RF, et al. MRI T2 and T1ρ relaxation in patients at risk for knee osteoarthritis: a systematic review and meta-analysis. BMC Musculoskelet Disord 2019;20:182–182. [PubMed: 31039785]
8. Nieminen MT, Rieppo J, Töyräs J, et al. T2 relaxation reveals spatial collagen architecture in articular cartilage: A comparative quantitative MRI and polarized light microscopic study. Magn Reson Med 2001;46:487–493. [PubMed: 11550240]
9. Keenan KE, Besier TF, Pauly JM, et al. Prediction of glycosaminoglycan content in human cartilage by age, T1ρ and T2 MRI. Osteoarthritis Cartilage 2011;19:171–179. [PubMed: 21112409]
10. Menezes NM, Gray ML, Hartke JR, Burstein D. T2 and T1ρ MRI in articular cartilage systems. Magn Reson Med 2004;51:503–509. [PubMed: 15004791]
11. Wyatt C, Kumar D, Subburaj K, et al. Cartilage T1rho and T2 relaxation times in patients with mild-to-moderate radiographic hip osteoarthritis. Arthritis Rheumatol 2015;67:1548–1556. [PubMed: 25779656]
12. Pedoia V, Gallo MC, Souza RB, Majumdar S. Longitudinal study using voxel-based relaxometry: Association between cartilage T(1ρ) and T(2) and patient reported outcome changes in hip osteoarthritis. J Magn Reson Imaging 2017;45:1523–1533. [PubMed: 27626787]
13. Gallo MC, Wyatt C, Pedoia V, et al. T(1ρ) and T(2) relaxation times are associated with progression of hip osteoarthritis. Osteoarthritis Cartilage 2016;24:1399–1407. [PubMed: 26973330]
14. Pedoia V, Li X, Su F, Calixto N, Majumdar S. Fully automatic analysis of the knee articular cartilage T1rho relaxation time using voxel-based relaxometry. J Magn Reson Imaging 2016;43:970–980. [PubMed: 26443990]
15. Russell C, Pedoia V, Amano K, Potter H, Majumdar S. Baseline cartilage quality is associated with voxel-based T1rho and T2 following ACL reconstruction: A multicenter pilot study. J Orthop Res 2017;35:688–698. [PubMed: 27138363]
16. Zhang Z, Castelló A. Principal components analysis in clinical studies. Ann Transl Med 2017;5:351–351. [PubMed: 28936445]
17. Jolliffe IT, Cadima J. Principal component analysis: a review and recent developments. Philosophical transactions Series A, Mathematical, physical, and engineering sciences 2016;374:20150202. [PubMed: 26953178]
18. Huang L, Reiss PT, Xiao L, Zipunnikov V, Lindquist MA, Crainiceanu CM. Two-way principal component analysis for matrix-variate data, with an application to functional magnetic resonance imaging data. Biostatistics 2017;18:214–229. [PubMed: 27578805]
19. Saravanakumar S, Thangaraj P. A computer aided diagnosis system for identifying Alzheimer's from MRI scan using improved Adaboost. J Med Syst 2019;43:76. [PubMed: 30756191]

20. Radulescu AR, Mujica-Parodi LR. A principal component network analysis of prefrontal-limbic functional magnetic resonance imaging time series in schizophrenia patients and healthy controls. Psychiatry Res 2009;174:184–194. [PubMed: 19880294]
21. Pedoia V, Russell C, Randolph A, Li X, Majumdar S, Consortium A-A. Principal component analysis-T(1ρ) voxel based relaxometry of the articular cartilage: a comparison of biochemical patterns in osteoarthritis and anterior cruciate ligament subjects. Quant Imaging Med Surg 2016;6:623–633. [PubMed: 28090441]
22. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502. [PubMed: 13498604]
23. Kohn MD, Sassoon AA, Fernando ND. Classifications in brief: Kellgren-Lawrence classification of osteoarthritis. Clin Orthop Relat Res 2016;474:1886–1893. [PubMed: 26872913]
24. Nilsdotter AK, Lohmander LS, Klassbo M, Roos EM. Hip disability and osteoarthritis outcome score (HOOS)--validity and responsiveness in total hip replacement. BMC Musculoskelet Disord 2003;4:10. [PubMed: 12777182]
25. Dobson F, Hinman RS, Hall M, Terwee CB, Roos EM, Bennell KL. Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review. Osteoarthritis Cartilage 2012;20:1548–1562. [PubMed: 22944525]
26. Rydevik K, Fernandes L, Nordsletten L, Risberg MA. Functioning and disability in patients with hip osteoarthritis with mild to moderate pain. J Orthop Sports Phys Ther 2010;40:616–624. [PubMed: 20811166]
27. Stratford PW, Kennedy DM, Woodhouse LJ. Performance measures provide assessments of pain and function in people with advanced osteoarthritis of the hip or knee. Phys Ther 2006;86:1489–1496. [PubMed: 17079748]
28. Li X, Wyatt C, Rivoire J, et al. Simultaneous acquisition of T1rho and T2 quantification in knee cartilage: repeatability and diurnal variation. J Magn Reson Imaging 2014;39:1287–1293. [PubMed: 23897756]
29. Lee S, Nardo L, Kumar D, et al. Scoring hip osteoarthritis with MRI (SHOMRI): A whole joint osteoarthritis evaluation system. J Magn Reson Imaging 2015;41:1549–1557. [PubMed: 25139720]
30. Neumann J, Zhang AL, Schwaiger BJ, et al. Validation of scoring hip osteoarthritis with MRI (SHOMRI) scores using hip arthroscopy as a standard of reference. Eur Radiol 2019;29:578–587. [PubMed: 29987419]
31. Shamonin D, Bron E, Lelieveldt B, Smits M, Klein S, Staring M. Fast parallel image registration on CPU and GPU for diagnostic classification of Alzheimer's disease. Front Neuroinform 2014;7:50. [PubMed: 24474917]
32. Klein S, Staring M, Murphy K, Viergever MA, Pluim JPW. elastix: A toolbox for intensity-based medical image registration. IEEE Trans Med Imaging 2010;29:196–205. [PubMed: 19923044]
33. Pedoia V, Lansdown DA, Zaid M, et al. Three-dimensional MRI-based statistical shape model and application to a cohort of knees with acute ACL injury. Osteoarthritis Cartilage 2015;23:1695–1703. [PubMed: 26050865]
34. Souza RB, Kumar D, Calixto N, et al. Response of knee cartilage T1rho and T2 relaxation times to in vivo mechanical loading in individuals with and without knee osteoarthritis. Osteoarthritis Cartilage 2014;22:1367–1376. [PubMed: 24792208]
35. Sophia Fox AJ, Bedi A, Rodeo SA. The basic science of articular cartilage: structure, composition, and function. Sports health 2009;1:461–468. [PubMed: 23015907]
36. Constantinou M, Loureiro A, Carty C, Mills P, Barrett R. Hip joint mechanics during walking in individuals with mild-to-moderate hip osteoarthritis. Gait Posture 2017;53:162–167. [PubMed: 28167387]
37. Kumar D, Wyatt C, Chiba K, et al. Anatomic correlates of reduced hip extension during walking in individuals with mild-moderate radiographic hip osteoarthritis. J Orthop Res 2015;33:527–534. [PubMed: 25678302]

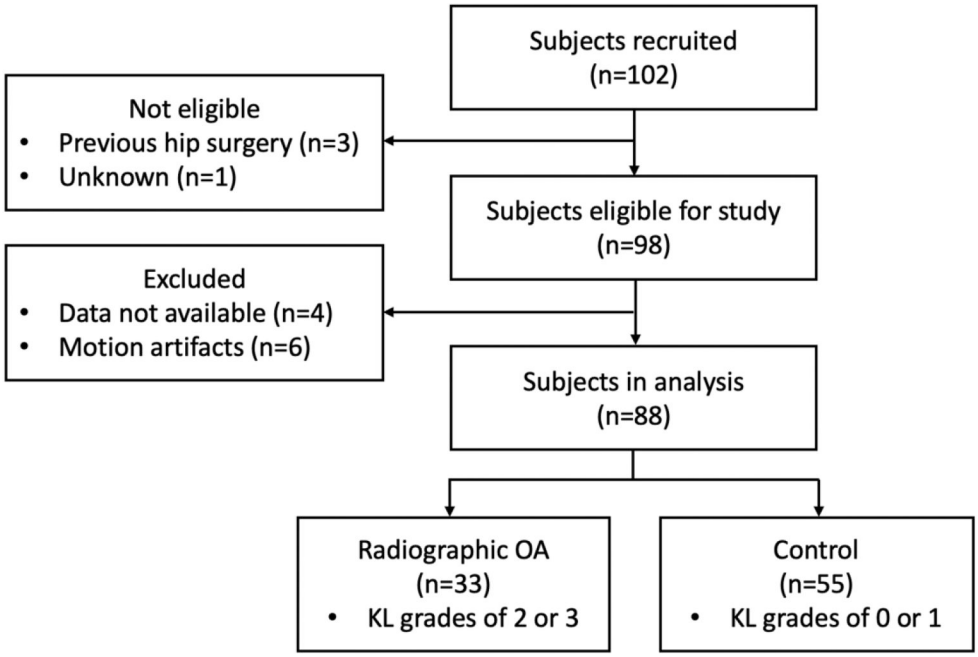

Figure 1.
Flowchart of subject enrollment. KL grade, Kellgren-Lawrence grading for radiographic osteoarthritis; OA: osteoarthritis.

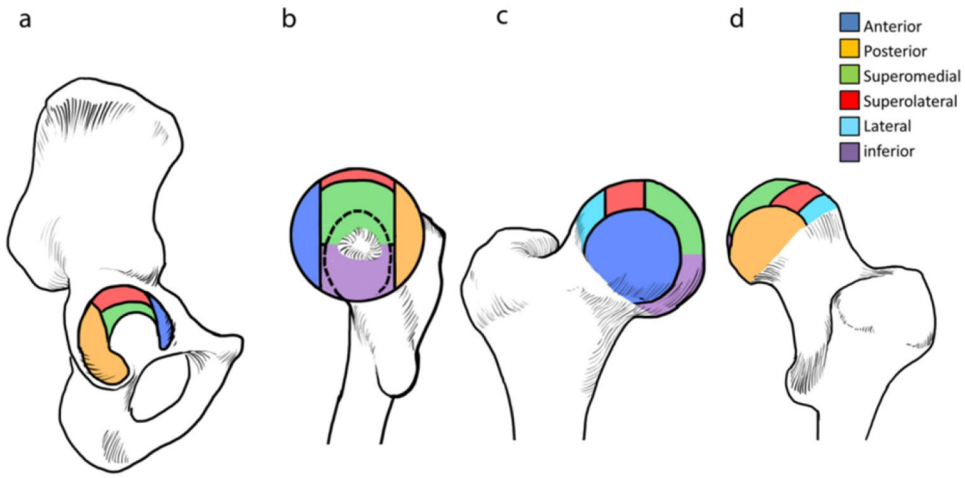

Figure 2.

Hip joint subregions for the grading of Scoring Hip OA with MR imaging. (A) Acetabulum joint subregions seen from lateral aspect. Femur joint subregions seen from (B) medial aspect, (C) anterior aspect, and (D) posterior aspect. Reproduced with permission from Kumar et al., J Orthop Res, 2015.

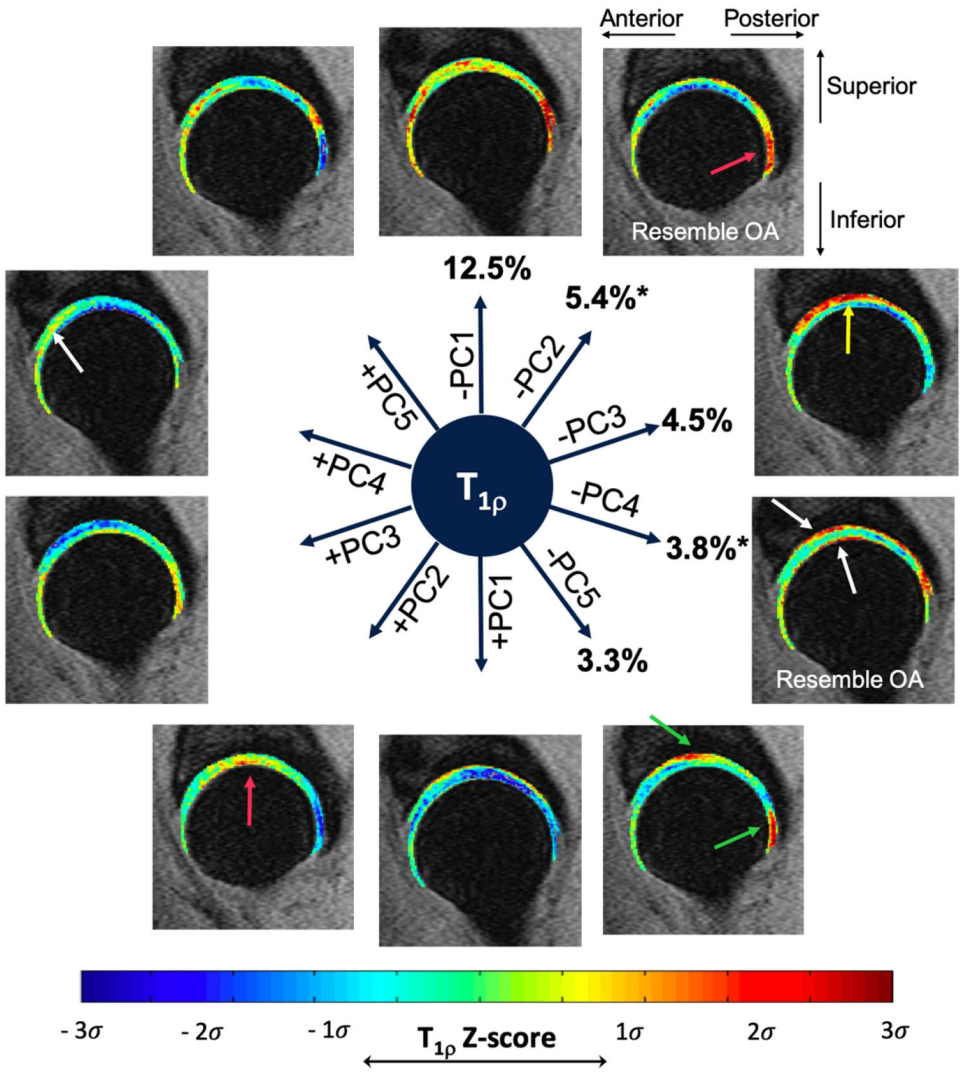

Figure 3.

Illustration of the first 5 principal components (PCs) extracted from the Z-score $T_{1\rho}$ mapping. Each PC is visualized at mean ± 3 mode variance. Mode 1: global elevation; mode 2: elevation in inferoposterior vs. central region (pink arrow); mode 3: elevation in acetabular (yellow arrow); mode 4: elevation in superficial *vs.* deep layer (white arrow); mode 5: elevation in inferoposterior and central regions (green arrow). * indicates PC mode to be significant predictor of the OA *vs.* control group classification.

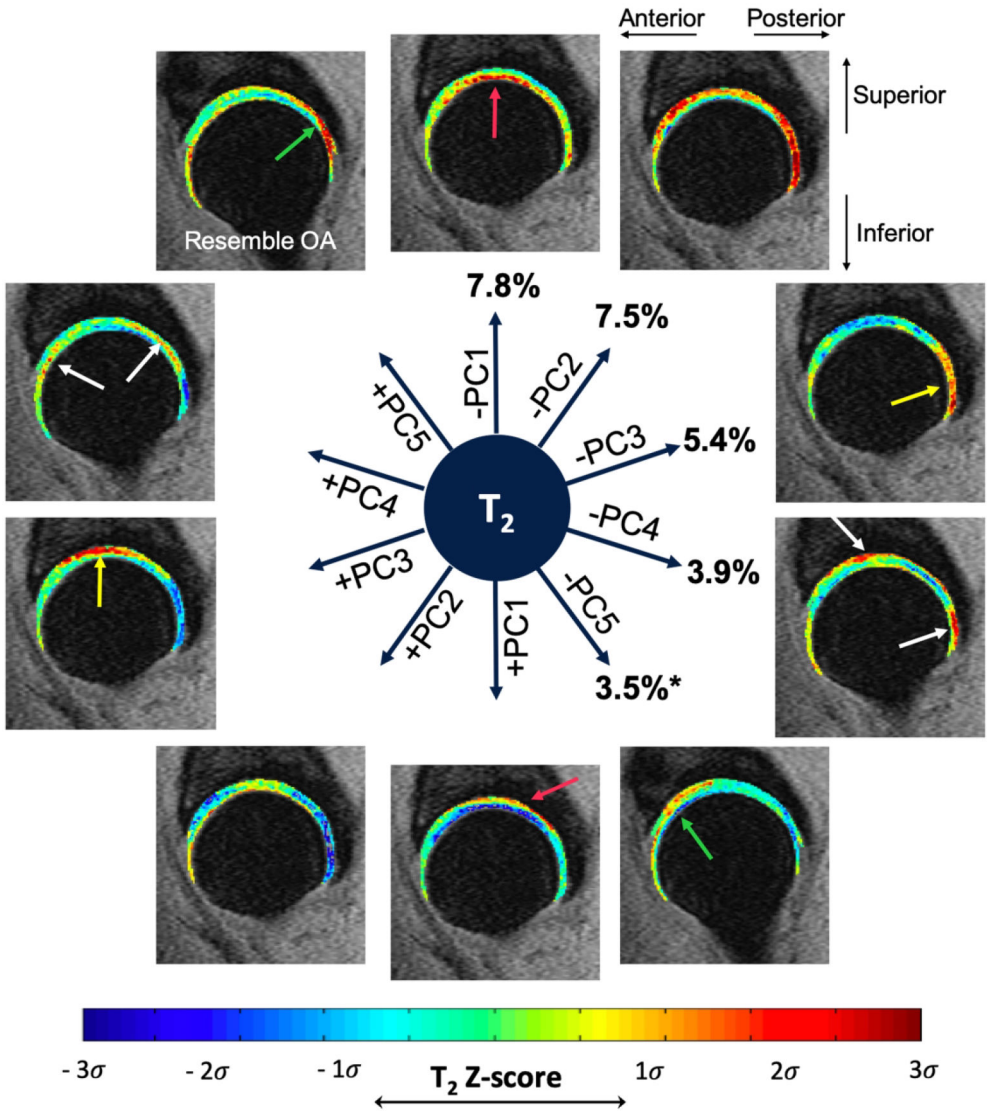

Figure 4.

Illustration of the first 5 principal components (PCs) extracted from the Z-score T_2 mapping. Each PC is visualized at mean ± 3 mode variance. Mode 1: elevation in femoral vs. acetabular (pink arrow); mode 2: global elevation; mode 3: posterior vs. central region (yellow arrow); mode 4: acetabular vs. deep layer (white arrow); mode 5: anterior vs. posterior (green arrow). * indicates PC mode to be significant predictor of the OA *vs.* control group classification.

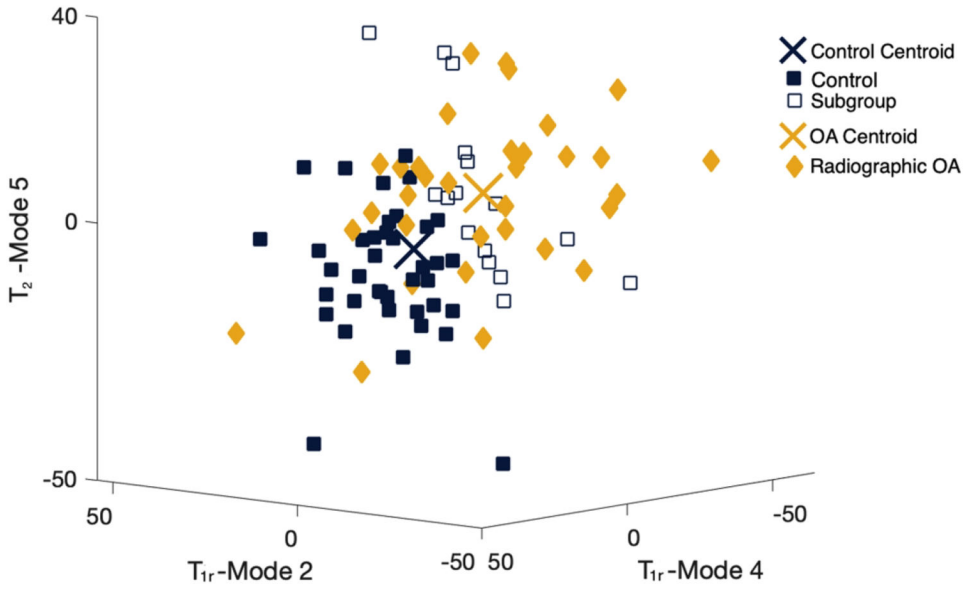

Figure 5.

Principal component plots based on the 3 modes that significantly predicted the radiographic OA *vs.* control group classification.

Table 1.

Demographics, patient-reported symptoms, physical function, and cartilage lesions in the radiographic osteoarthritic and control groups.

	Radiographic OA (n=33)	Control (n=55)	p value
Demographics			
Sex, n[†]	20 males, 13 females	28 males, 27 females	0.507
Age, y	50.2 ± 13.3	41.3 ± 12.0	**0.002**
BMI, kg/m^2	23.5 ± 3.0	24.0 ± 3.1	0.478
KL grade (0-4)[‡]	20 KL=2, 13 KL=3	26 KL=0, 29 KL=1	N/A
HOOS, %			
Pain	83.2 ± 21.1	93.8 ± 12.7	**0.005**
Symptoms	79.6 ± 24.6	92.2 ± 12.1	**0.003**
Daily activity	87.5 ± 19.4	95.9 ± 11.0	**0.014**
Sports	81.4 ± 25.8	93.9 ± 12.6	**0.004**
Quality of life	75.9 ± 28.7	89.1 ± 17.1	**0.010**
Physical Function			
TUG, s	6.3 ± 0.9	5.9 ± 0.9	0.070
6MWT, m	610.0 ± 97.7	638.8 ± 89.3	0.174
Subjects with Lesions, n (%)[†](SHOMRI ≥ 1)			
Acetabular			
Superolateral	18 (54.5)	8 (14.5)	**<0.001**
Superomedial	9 (27.2)	10 (18.1)	0.600
Anterior	15 (45.4)	10 (18.1)	**0.021**
Posterior	5 (15.1)	2 (3.6)	**0.007**
Total	22 (66.6)	19 (34.5)	**0.046**
Femoral			
Lateral	16 (48.4)	11 (20.0)	**0.011**
Superolateral	14 (42.4)	13 (23.6)	**0.018**
Superomedial	11 (33.3)	12 (21.8)	0.488
Inferomedial	5 (15.1)	6 (10.9)	0.560
Anterior	13 (39.3)	8 (14.5)	**0.015**
Posterior	5 (15.1)	5 (9.0)	0.282
Total	23 (69.6)	28 (50.9)	**0.034**

Data presented as mean ± SD. Abbreviations: 6MWT, six-minute walk test; BMI, body mass index; KL, Kellgren-Lawrence; HOOS, Hip injury and Osteoarthritis Outcome Scores; SHOMRI, Scoring Hip OA with MR imaging; TUG, Timed Up and Go.

[†]Indicates chi-square analysis

[‡]Subjects with KL grade equaled to 4 were excluded from the study.

Table 2.

Summary of the results of the logistic regression model used to identify the predictors of radiographic OA *vs.* control group classification for the first 5 PCs from each $T_{1\rho}$ and T2 map. Only significant predictors were listed here.

Group Classification (radiographic OA *vs.* controls)				
$T_{1\rho}$ Mapping	**Estimate**	**SE**	**tStat**	**p value**
Intercept	1.558	0.571	2.727	0.007
PC2	−0.006	0.002	−2.545	0.012
PC4	−0.010	0.002	−3.386	0.001
BMI	−0.048	0.017	−2.681	0.008
Prediction model summary:				
88 observations, 79 error degrees of freedom				
Estimated Dispersion: 0.188				
F-statistic *vs.* constant model: 3.86, p value=0.000699				
T2 Mapping				
Intercept	1.539	0.543	2.834	0.005
PC5	0.014	0.003	4.591	1.638e-05
Age	0.010	0.003	2.677	0.009
BMI	−0.054	0.017	−3.093	0.002
Prediction model summary:				
88 observations, 79 error degrees of freedom				
Estimated Dispersion: 0.174				
F-statistic *vs.* constant model: 4.93, p value=5.72e-05				

Abbreviations: BMI, body mass index; OA: Osteoarthritis.

Table 3.

Summary of the results of the logistic regression model used to identify the predictors of radiographic OA *vs.* control group classification with $T_{1\rho}$ and T_2 averages within the region of interests (ROIs).

Group Classification (radiographic OA *vs.* controls)				
ROI Averages	**Estimate**	**SE**	**tStat**	**p value**
Intercept	6.407e-05	0.907	7.062e-05	0.999
$T_{1\rho}$ Femoral	−0.028	0.028	−1.030	0.305
$T_{1\rho}$ Acetabular	0.031	0.028	1.096	0.276
T_2 Femoral	0.017	0.022	0.792	0.430
T_2 Acetabular	0.007	0.027	0.265	0.791
Age	0.013	0.003	3.375	**0.001**
BMI	−0.034	0.018	−1.855	0.067
Sex	−0.116	0.117	−0.994	0.322
Prediction model summary:				
88 observations, 80 error degrees of freedom				
Estimated Dispersion: 0.212				
F-statistic *vs.* constant model: 2.48, p value=0.0237				

Table 4.

Demographics, patient-reported symptoms, physical function, and cartilage lesions between a subgroup of subjects with compositional abnormalities and remaining controls.

	Subgroup (n=16)	Control (n=39)	p value
Demographics			
Sex, n†	9 males, 7 females	19 males, 20 females	0.612
Age, y	42.7 ± 13.6	40.7 ± 11.44	0.588
BMI, kg/m^2	25.2 ± 3.1	23.5 ± 3.0	0.068
KL grade (0-4)	8 KL=0, 8 KL=1	18 KL=0, 21 KL=1	0.795
HOOS, %			
Pain	96.2 ± 7.6	92.8 ± 14.4	0.379
Symptoms	94.6 ± 7.6	91.1 ± 13.6	0.332
Daily activity	95.5 ± 8.8	96.1 ± 12.0	0.854
Sports	94.5 ± 9.6	93.7 ± 13.9	0.840
Quality of life	92.1 ± 14.3	87.8 ± 18.2	0.404
Physical Function			
TUG, s	6.5 ± 1.1	5.7 ± 0.7	**0.003**
6MWT, m	626.4 ± 93.7	644.0 ± 88.2	0.527
Subjects with Lesions, n (%)†(SHOMRI ≥ 1)			
Acetabular			
Superolateral	3 (18.7)	5 (12.8)	0.571
Superomedial	5 (31.2)	5 (12.8)	0.274
Anterior	4 (25.0)	6 (15.3)	0.267
Posterior	0 (0.0)	2 (5.1)	0.356
Total	7 (43.7)	12 (30.7)	0.658
Femoral			
Lateral	7 (43.7)	4 (10.2)	**0.009**
Superolateral	4 (25.0)	9 (23.0)	0.771
Superomedial	3 (18.7)	9 (23.0)	0.878
Inferomedial	4 (25.0)	2 (5.1)	**0.032**
Anterior	2 (12.5)	6 (15.3)	0.783
Posterior	1 (6.2)	4 (10.2)	0.433
Total	8 (50.0)	20 (51.2)	0.448

Data presented as mean ± SD. Abbreviations: 6MWT, six-minute walk test; BMI, body mass index; KL, Kellgren-Lawrence; HOOS, Hip injury and Osteoarthritis Outcome Scores; SHOMRI, Scoring Hip OA with MR imaging; TUG, Timed Up and Go.

†Indicates chi-square analysis.