Title

MR study of longitudinal variations in proximal femur 3D morphological shape and associations with cartilage health in hip osteoarthritis

Journal

Journal of Orthopaedic Research®, 37(1)

ISSN

0736-0266

Authors

Inamdar, Gaurav

Pedoia, Valentina

Rossi-Devries, Jasmine

et al.

Publication Date

2019

DOI

10.1002/jor.24147

Peer reviewed

HHS Public Access

Author manuscript

J Orthop Res. Author manuscript; available in PMC 2019 March 22.

Published in final edited form as:

J Orthop Res. 2019 January ; 37(1): 161–170. doi:10.1002/jor.24147.

MR Study of Longitudinal Variations in Proximal Femur 3D Morphological Shape and Associations With Cartilage Health in Hip Osteoarthritis

Gaurav Inamdar[1], **Valentina Pedoia**[1], **Jasmine Rossi-Devries**[1], **Michael A. Samaan**[1], **Thomas M. Link**[1], **Richard B. Souza**[1,2], and **Sharmila Majumdar**[1]

[1]Department of Radiology and Biomedical Imaging, University of California-San Francisco, 1700 Fourth Street, Suite 203, QB3 Building, San Francisco 94107, California

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

Abstract

The goal of this study was to use quantitative MRI analysis to longitudinally observe the relationship between 3D proximal femur shape and hip joint degenerative changes. Forty-six subjects underwent unilateral hip MR imaging at three time points (baseline, 18 and 36 months). 3D shape analysis, hip cartilage $T_{1\rho}/T_2$ relaxation time quantification, and SHOMRI MRI grading were performed at each time point. Subjects were grouped based on KL, SHOMRI, and HOOS pain scores. Associations between these score groupings, time, and longitudinal variation in shape, were analyzed using a generalized estimating equation. One-way ANCOVA was conducted to evaluate change in shape as a predictor of the worsening of degenerative changes at 36 months. Our results demonstrated that subjects displayed an increase in the volume of the femoral head and neck (Mode 3) over time. This shape mode was significantly more prevalent in patients that reported pain. Longitudinal changes in this shape mode also served as borderline predictors of elevated $T_{1\rho}$ values ($p = 0.055$) and of cartilage lesions ($p = 0.068$). Subjects showed a change in the Femoral Neck Anteversion angle (FNA) over time (Mode 6). This shape mode showed a significant interaction with the presence of cartilage lesions. The results of this study suggest that specific variations in bone shape quantified through 3D-MRI based Statistical Shape modeling show an observable relationship with hip joint compositional and morphological changes. The shapes observed lead to early degenerative changes, which may lead into OA, thus confirming the important role of bone shape changes in the pathogenesis of OA.

Keywords

osteoarthritis; bone shape; statistical shape modeling (SSM); hip; MRI

Correspondence to: Gaurav Inamdar (T: 925-895-9214; F: 415-353-9423; gaurav.inamdar1995@gmail.com).

AUTHORS' CONTRIBUTIONS

Conception and design: Valentina Pedoia and Sharmila Majumdar. Collection and processing of data: Gaurav Inamdar, Valentina Pedoia, Jasmine Rossi-Devries. MRI grading: Thomas M. Link. Analysis and interpretation of the data: Gaurav Inamdar, Valentina Pedoia, Sharmila Majumdar, Michael A. Samaan, Richard B. Souza. Drafting of the article: Gaurav Inamdar. Obtaining funding: Sharmila Majumdar and Richard B. Souza. Final approval of the article: All the authors.

Osteoarthritis (OA) is a debilitating disease adversely affecting millions of people around the world.[1] OA of the hip and the knee in particular have been seen to cause a large loss in the quality of life of patients, and has a large and far reaching economic and social impact.[2]

Previous studies have established that the early stages of OA are characterized by proteoglycan loss, thinning and disruption of collagen, and changes in hydration; while late stages include dehydration and loss of cartilage accompanied by bone deformation.[3]

Several measurements extracted from imaging have been used in previous studies to characterize the existence and progression of OA.[4] One frequently used measure is the radiographic grading system known as the Kellgren–Lawrence (KL) scale.[5] The KL score takes into account osteophyte formation and joint space narrowing to determine the presence of OA. However, radiographic measurements often reflect late stage OA and other measurements are required to measure earlier stages of OA.[6] Previous studies have established the effectiveness of MRI to assess morphological abnormalities in the hip joint using scoring systems such as the Scoring Hip Osteoarthritis with MRI (SHOMRI) scoring system.[7] Quantitative compositional MRI tools such as $T_{1\rho}$ and T_2 relaxation times provide information on proteoglycan and collagen content as well as cartilage collagen orientation and are found to be elevated in people with OA.[8–11] Previous studies have shown a longitudinal relationship between elevation in $T_{1\rho}$ and T_2 and the development of cartilage lesions, indicating that $T_{1\rho}$ and T_2 may be good biomarkers of the progression of OA.[12]

In addition to biochemical and morphological cartilage alterations, bone shape changes of the hip and knee joints have shown to be present in OA.[13] Abnormal bone remodeling and abnormal repair of bone tissue have long been known to be factors in OA as abnormalities such as osteophytes and bone marrow lesions are highly prevalent in patients suffering from OA.[13] Abnormal densification and growth in the subchondral bone in particular has been shown in previous studies to be related to the progression of OA.[13] These abnormalities can lead to changes in biomechanics and changes in the loading of force on the joint.[14] Therefore, understanding the remodeling process over time and how this process changes bone shape is critical to fully understanding the progression of OA. To better understand and observe bone shape of the hip and the knee in relation to OA and joint degeneration, previous studies have used radiographic measurement to observe changes in specific bone shape landmarks.[15] Another method that has been used more frequently is Statistical Shape Modeling (also known as Active Shape Modeling), which allows for complex shapes to be represented without making A priori assumptions.[16] Previous studies have established the viability of using SSM techniques to model bone.[17] Statistical shape modeling (SSM) has been used in a 2D setting to provide a larger picture of whole bone shape[18–20] of the hip and knee and has traditionally been conducted using radiographs. Recently there has been interest in using 3D statistical shape modeling (SSM) methods[21–25] on MRI and CT images. 3D SSM methods provide a more comprehensive understanding of shape features than traditional 2D methods, which can be affected by joint positioning during scanning. 3D-MRI based SSM techniques have been recently used to determine if bone shape features can serve as a biomarker of OA by comparing bone shape to cartilage morphology and biochemical properties.[25]

Despite the large amount of work done in the past few years to better understand the cartilage and bone interactions and their role in OA pathogenesis, most of these studies have been of a cross sectional design and little research has been done to observe the longitudinal change in bone shape and its association with the progression of OA. This study aims to study longitudinal changes in bone shape of the proximal femur using 3D shape modeling applied to MR images to quantify if bone shape changes are related to changes in measures of cartilage health and osteoarthritis of the hip joint.

We hypothesize that we will be able to observe bone shape modes that will change over time and show an association with measures of radiographic OA (SHOMRI), symptomatic OA (HOOS), morphological and compositional joint abnormalities as measured with the SHOMRI scoring system, and with $T_{1\rho}$ and T2 relaxation times. We also hypothesize that the change of bone shape over a period of 36 months will show an association with the progression of OA, and the worsening of symptomatic OA at 36 months as measured by worsening of SHOMRI scores, elevation of $T_{1\rho}$ values, and worsening of HOOS scores.

MATERIALS AND METHODS

This is an analytic study (level of evidence: III). All subjects involved in the study provided written informed consent. All study protocols were conducted in accordance with the regulations set forth by the committee for human research at the University of California, San Francisco.

Subjects

Subjects were selected from a longitudinal study on hip OA including a baseline visit and two follow-ups after 18 and 36 months. Participants were excluded based on the following criteria: Below the age of 18, previous hip trauma, inflammatory arthritis, sickle cell disease, hemochromatosis, hemoglobinopathy, hip joint KL score >3, contraindications to MRI, radiographic evidence of femoroacetabular impingement, and any disability which would preclude the subject from performing dynamic tasks used to assess joint function.

KL scores were assigned by an experienced musculoskeletal radiologist on weight bearing anterior-posterior radiographs. The hip with the higher KL score underwent an MRI. If the KL scores for both hips were the same, the more symptomatic side was chosen to undergo an MRI.

Patients also provided self-reported Hip Disability and Osteoarthritis Outcome Scores (HOOS) at baseline, 18 months, and 36 months. The HOOS scores were used to assess the pain and function of the hip joint and allowed a better understanding into the progression and effects of symptomatic OA.[26]

MR Imaging Protocol and Morphological Grading

Imaging was conducted at each visit on a 3T MRI scanner (GE MR750; GE Healthcare, Waukesha, WI) using an eight-channel receive-only coil (GE Healthcare). Subjects were positioned supine and hip joint position was standardized: Feet were slightly internally rotated and taped together to prevent movement during the scan.[25] One MR-sequence

obtained was a combined $T_{1\rho}$ and T_2 sequence which was acquired in a sagittal orientation with a field of view of 14 cm, matrix size of 256 × 128 pixels, slice thickness of 4 mm, recovery time of 1.2 s, bandwidth of 62.5 kHz, no gap, in-plane resolution of 0.5 mm and acquisition time of 13:47; time of spin lock (TSL) = 0/15/30/45 ms, and spin-lock TE = 0/10.4/20.8/41.7.[12] The another MR-sequence that was obtained was the 2D Fast-Spin echo (FSE) which was acquired with a repetition time of 2400–3700 ms, echo time of 60 ms, field of view of 14–20 cm, matrix size of 288 × 224 pixels, slice thickness of 3–4 mm.[7] Semi-quantitative clinical grading of acetabular and femoral cartilage abnormalities was performed using the Scoring Hip Osteoarthritis with MRI (SHOMRI) scoring system.[7]

Image Processing: 3D Shape Analysis

All Image processing was performed in Matlab (The Mathworks, Natick, MA) using in-house programs. MR imaging studies were segmented using a single atlas based method as described in Pedoia et al.[27] Segmentation was conducted on proximal femurs of all the subjects for every time point using a $T_{1\rho}$-weighted image. A single user (GI) conducted quality control on all the segmentations and manually corrected any errors present in the atlas based method. Using the segmented image datasets, 3D-SSM was conducted as previously described and evaluated.[28,29]

Image Processing: $T_{1\rho}/T_2$ Quantification

$T_{1\rho}$ and T_2-weighted images were rigidly registered to the first $T_{1\rho}$-weighted image (TSL = 0) using the VTK CISG Registration Toolkit (Kitware Inc, Clifton Park, NY) as previously described.[12] Semi-automatic segmentation of the cartilage was conducted as previously described[29] and slices that had severe effects of partial volume were excluded from segmentation. The hip joint was divided into eight subcompartments and in each subcompartment the $T_{1\rho}$ and T_2 relaxation times were computed by averaging all the voxels in the sub-compartment.[30] Any subregion with fewer than 50 pixels over all segmented slices was excluded.[12]

Subjects Grouping

The first aim of this study was to investigate whether there are any bone shape modes that change over time and to find out if the shape changes showed any observable relationship to any of the measures of OA and joint degeneration used in this study. To accomplish this, patients were stratified based on radiographic evidence of OA with patients having a KL score of 0 and 1 classified as having no OA, subjects with a KL of two classified as having mild OA and subjects with a KL of three classified as having moderate OA. Patients of KL 0 and 1 were grouped together and labeled as having no OA as by the KL scoring system these patients do not show definite joint space narrowing or osteophyte formation and do not meet the criteria of definite radiographic OA. Subjects with a SHOMRI cartilage subscore greater than 1 in any subcompartment at any time point, were defined as having cartilage lesions. Subjects with HOOS pain subscores below 90 at any time point were classified as having pain. Patients with $T_{1\rho}$ values more than 2SD of the average of any sub compartment at the baseline time point were classified as having elevated $T_{1\rho}$ values.

The second aim of this study was to observe if any change in shape modes exist which can be used as predictors of OA progression. To accomplish this subjects who showed an increase of one or more in the total SHOMRI cartilage score between baseline and 36 months were classified as SHOMRI progressors. SHOMRI scores were calculated in both the acetabular and femoral cartilage subcompartments. $T_{1\rho}$ progression was by comparing each subject against a control group, which comprised of individuals who showed a KL of either 0 or 1 with no increase in the total SHOMRI score between baseline and 36 months. The average $T_{1\rho}$ values were computed for each sub compartment of the control group. Any subject that resided outside of 2SD in any sub-compartment at the 18 month or 36 month time point were class was classified as a $T_{1\rho}$ progressors.

Statistical Analysis

The first 10 bone shape modes describing 85.6% of the overall variation were observed and were fit to a generalized estimating equation (GEE model) to determine any relationship between change in bone shape modes and time. Group interactions between change over time of the shape modes and SHOMRI scores, KL scores, HOOS scores, and $T_{1\rho}$ values were also considered. In addition, change in the first 36 months of shape modes which showed a significant relationship with time were observed to possibly have an association with changes in measures of OA through one-way ANCOVA analysis. Demographic parameters such as age at baseline, gender, and BMI were considered as adjusting factors in all the analyses. To confirm the observation done with the ANCOVA, Pearson's correlation was run between the change in total SHOMRI cartilage sub score and $T_{1\rho}$ global femoral averages between the baseline and 36 month time points. A *p*-value of 0.05 was considered significant.

RESULTS

Forty-six subjects (25 male, 21 Female) were included in this study (age 47.6 13.4, BMI 27.2 2.57 kg/m^2). The patient cohort was stratified based on the rules mentioned above and is shown in Table 1.

Patients were also grouped according to KL scores to determine severity of OA (Table 2).

The first 10 Modes were seen to account for a majority of the variability seen among the patient cohort and were compared to time through a GEE model (Table 3). Modes 3, 4, 6, and 10 initially showed a significant relationship with time. However, after adjusting for demographic factors, solely Mode 6 demonstrated a significant relationship with time (Table 4). Mode 3 in particular no longer appeared significant due to a strong correlation between Mode 3 and Gender. Modes 4 and 10 were removed to better focus our study on bone shape changes due to joint degeneration and possible OA. This is because modes 4 and 10 did not show any interaction with measures of OA. The changes in Mode 4 and Mode 10 may be due to gender, BMI, and age differences and it is also possible that Mode 4 and Mode 10 are shape changes that occur simply due to the aging process. A larger data set is required to appropriately study aging effects and other demographic effects and is outside the scope of this study. Although Mode 3 was correlated to gender, it was still included as Mode 3 showed a relationship with parameters of joint degeneration as seen in Table 5.

GEE results on the groupings interactions outlined in Table 1 showed a significant relationship between Mode 3 HOOS pain *time (p-value = 0.023), Table 5. The MR metrics ($T_{1\rho}$ values) did not show a significant change over time with all modes including Modes 3 and 6.

Modes 3 and 6 were visualized at ±3 SD from the average mode values to better understand the changes seen in the mode (Fig. 1). Figure 1 shows screenshots best illustrating the shape changes seen in the 3D visualization of the modes generated in Matlab. The image shown is a synthetic image generated to visualize the changes in shape associated with the change in values of the shape modes. At baseline the visualization is generated to be −3 SD from the average shape of all the hip joints at baseline. Similarly the 3D visualizations at 36 months are +3 SD from the average shape values of the hip joints at 36 months. Viewing the baseline image at the lower bounds of −3 SD and the 36-month image at the upper bounds of +3 SD allows Figure 1 to capture the full range of change that is seen among the hips in the data set between the two time points. The shape changes observed in reality are smaller and more varied from hip to hip. Viewing the visualization at ±3 SD ensures that the variability within the data set is represented on the visualization and is presented to the reader in an easy to understand format. The figure is meant to serve as a visual guide to help the reader better understand the bone shape features associated with the mode values for Modes 3 and 6 at both the baseline and 36 month time point. As seen in Figure 1, Mode 3 was seen to relate to the volume of both the femoral head and the femoral neck. Lower mode values corresponded to a more voluminous femoral head and neck (Fig. 1a). Mode 6 was seen to relate to the Neck Anteversion angle. Smaller mode values showed a femoral neck, which was angled more posterior to the shaft when compared to higher mode values, which were more, angled toward the anterior when compared to the shaft (Fig. 1b).

The average mode values for Modes 3 and 6 were observed at all three time points (Fig. 2). Both modes show a decrease in the average mode value demonstrating that an overall trend toward the shape seen with smaller mode values for Mode 3: Increase in the volume of femoral head and neck; and Mode 6: change in the axial shaft angle towards the posterior direction.

The average percent change between baseline and 36 months was observed for each grouping for Mode 3 and Mode 6 as well. For Mode 3 it was seen that a larger average percent change was seen in the group classified as having no pain (−28.36 ± 31% change) when compared to the group that was classified as having pain (−8.59 ± 27.36% change) (Fig. 3).

Mode 6 was observed to have a significant relationship between SHOMRI scores *time (p-value = 0.025) and the average percent change between of the group classified with high SHOMRI scores (−37.36% ± 37.04% change) was much larger than the percent change in the low SHOMRI scores group (−4.52% ± 31.00% change). In addition, a higher percent difference was seen in the high KL group (−20.83% ± 38.81% change) and the elevated $T_{1\rho}$ group (−14.38% ± 42.36%) (Fig. 4). These relationships, however, were not seen to be significant by the GEE model (Table 3).

To fulfill our second aim of the study, we observed if any of the mode values were associated with worsening in radiographic and symptomatic OA. Worsening of OA was determined by worsening of SHOMRI, HOOS, and $T_{1\rho}$ values as described above. The patient cohort was divided into progressors and non progressors ($N = 44$). Two subjects were excluded, as they did not possess the necessary demographic information and mode values. The final groupings for progressors and non progressors is shown in Table 6. Two subjects were excluded as they did not posses all the necessary demographic information for categorization. Among the SHOMRI progressors seven patients progressed only in the acetabular compartment, seven in only the femoral compartment, and eight in both compartments. However the patients that only progressed in the acetabular side were still included as changes in the proximal femur could potentially lead to cartilage degeneration at any place in the hip joint through loading forces. By including both femoral and acetabular cartilage progressors we can observe the overall cartilage health of the joint when Modes 3 and 6 are present. No formal statistical analysis was conducted between the groups of progressors due to the small sample size of each group. However, it was seen that there was no significant difference between Modes 3 and 6 values among any of the three groups of progressors.

On the progressor and non-progressor groups, a one-way ANCOVA analysis for the progressor/non-progressor groups was run using age at baseline, gender, and BMI as adjustments. The results are shown in Table 7. SHOMRI scores ($p = 0.068$) as well as $T_{1\rho}$ progressors ($p = 0.055$) showed a borderline significant relationship with Mode 3. For confirmation, a Pearson's correlation was run between Mode 3, change in total cartilage SHOMRI scores, and $T_{1\rho}$ values. For SHOMRI scores and $T_{1\rho}$ values, a modest correlation of $R = 0.32$, $R = 0.21$ respectively was observed. Mode 6 was not found to be a significant predictor of the progression of OA as no relationship with any measure was seen.

DISCUSSION

Our study employs and further confirms the viability of 3D statistical shape modeling techniques to observe and quantify bone shape changes from MRI images and adds to the body of studies, which have successfully used 3D SSM techniques to study OA.[23–25] Various previous studies using both radiographs and MR images have shown a link between bone shape and OA.[31–33] Our study builds on these results and demonstrates an observable relationship between bone shape changes and measures of OA and joint degeneration. Our study clearly demonstrates that even over a short period of 3 years, changes in bone shape are visible and measurable. In this study we observed that an increase in the volume of the femoral head and neck, as well as the a change in the neck anteversion angle is related to degeneration of the hip joint and is related to measures of OA and degenerative changes of the joint.

In this study, of the 10 shape modes observed, Modes 3 and 6 were analyzed in detail. The shape of Mode 3 (Fig. 1) showed a significant relationship with time and represented an increase in the volume of the femoral head and neck as time progressed. Previous studies have failed to reach a consensus on the relationship between an increase in the volume of the femoral neck and OA.[34–35] Our results demonstrated a relationship between the

development of Mode 3 and symptomatic pain (Fig. 4). In addition Mode 3 acted as a borderline predictor of worsening cartilage lesions ($p = 0.068$) and an elevation of T1p values ($p = 0.055$; Fig. 4). It is possible that the altered shape of Mode 3 impacts the loading of the joint and thus is able to reduce subjective pain scores. Further study of the biomechanics of patients with high Mode 3 values is required to understand the mechanism that leads to the development of the shape seen in Mode 3. One possible explanation for the increase in bone volume seen is due to possible growth of subchondral bone around the femoral neck and femoral head. Previous studies have established that a large increase in bone volume is often seen in areas where bone and cartilage meet.[35] In this area of the joint, the cartilage is susceptible to degeneration. The femoral head is an area that is constantly in contact with cartilage and an increase in volume in this area may be responsible for Mode 3 being a borderline predictor of cartilage lesions. In addition previous studies have demonstrated excess joint loading leading to changes in the density of subchondral bone tissue and an increase in bone remodeling.[36] It is possible that given the relationship observed between pain and Mode 3 that excess joint loading is leading to increased subchondral bone growth in patients in Mode 3. However this is a future direction of the study as presently no measurements of subchondral bone growth and content were taken. Several studies also propose the role of increased endochondral ossification in patients with OA, which would lead to cartilage being vascularized and mineralized into bone.[32] This would indicate that an increase in the volume of the femoral head would be causing the cartilage degeneration seen. Increased endochondral ossification is a key component of the development of osteophytes, which are used as a radiographic measure of OA.[33] These are two areas of future research for this study as no measurements of subchondral bone growth, or endochondral ossification growth was measured. This study establishes a relationship between Mode 3 and measures of OA and joint degeneration. However the mechanisms for the changes are not known at this time and are an area of further study. Further study of bone mineral content, subchondral and trabecular bone density, and composition is required to observe if either of the proposed theories describe the mechanism for the increase in the volume of the femoral head and neck as seen in Mode 3.

Higher Mode 6 values were seen to be related to the position of the femoral head in relation to the femoral shaft in the coronal plane. This angle is known as the Femoral Neck Anteversion angle (FNA) and is changed in higher Mode 6 values. Mode 6 showed a significant relationship with cartilage lesion scores, indicating that the changed angle of the femoral head is related to degeneration in the cartilage. In addition, a larger percent change in Mode 6 values were seen in patients showing various measures of joint degeneration such as KL scores, SHOMRI scores, and elevated $T_{1\rho}$ values indicating that the development of Mode 6 may be related to joint degeneration seen in OA (Fig. 4). However, Mode 6 did not act as a predictor of any of the measures of OA progression seen indicating that any changes to the FNA may occur alongside joint degeneration rather than as the cause of joint degeneration. Previous studies have shown that changes in FNA can lead to an alteration of biomechanics.[37] However, there is no general consensus on the relationship between the FNA and OA with studies both claiming an increased FNA is related and not related to OA.[37–38] Previous studies have been conducted on 2D radiographic and the 3D-SSM method used in this study may provide a clearer picture of the role of the FNA angle in OA.

However we cannot reliably comment on the mechanism of the changes seen as that is outside of the scope of this study. More studies, however, are required to see the effect on biomechanics and joint loading that occur when Mode 6 values are decreased.

This study is one of the few to look longitudinally at bone shape in relation to OA. In addition, the use of 3D-SSM techniques and several established measures of OA provides a more concrete and comprehensive picture of the health of the hip joint. By showing the feasibility of applying shape modeling on 3D MRI and the sensitivity of the technique to detecting changes even in short follow ups we bring to the OA imaging community a possible new imaging biomarker that potentially can track OA progression and identify subjects with accelerated joint degeneration. This could be of great interest to study population such as patients with FAI, who are at risk of Hip OA onset.

However, several limitations exist in the current study. Segmentation and analysis of bone shape was conducted using low-resolution images with a large slice thickness (4 mm). This led to 3D image reconstruction consisting of larger voxels. It is possible that the large voxel size of the study led to some more nuanced changes not being detected. Changes could have been missed in the medial and lateral margins of the proximal femur as these areas were out of plane to the image acquisition. Further studies using smaller isotropic voxels are necessary to determine if any shape changes in the medial and lateral margins were missed. In addition the low voxel size forced the study to focus only on the proximal femur and not the acetabular surface as well. Despite these limitations we are confident of the shape changes seen in Modes 3 and 6 as the changes observed are in the anterior posterior direction and are in plane to image acquisition. Another limitation of this study is the small sample size of 46 subjects. Follow-up studies on a larger patient cohort are necessary to confirm the results of this study. In particular a larger number of patients is required to understand the relationship between Modes 4 and 10 and various demographic parameters such as age, gender, and BMI. In addition we were unable to establish either mode as a predictor of worsening cartilage lesion scores, or of elevated T1p values. Change in Mode 3 acted only as a borderline predictor for both these measures due to inter variable associations among the variables considered for the ANCOVA analysis. Mode 3 showed a weak relationship with age which in the ANCOVA served to dilute the significance of Mode 3 and lead to it being only a borderline predictor. Further study is required to understand the relationship between Mode 3 and age that is seen.

In conclusion, this study establishes that the femoral neck anteversion angle and the volume of the femoral head and neck show an observable relationship to joint degeneration and show early stage changes in bone shape, which may develop into OA. This study further confirms that certain changes in joint shape are integral in the pathogenesis of joint degeneration and eventually the development of OA. Furthermore, this study demonstrates the validity and utility of 3D-SSM to quantify and track changes of bone shape in patients of OA.

ACKNOWLEDGMENTS

This study was supported by the NIH NIAMS P50, AR060752, and F32 AR069458. The content of this study is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Grant sponsor: Foundation for the National Institutes of Health;

Grant numbers: AR060752F32, AR069458, NIAMS P50.

REFERENCES

1. Berenbaum F, Eymard F, Houard X. 2013 Osteoarthritis, inflammation and obesity. Curr Opin Rheumatol 25: 114–118. [PubMed: 23090672]
2. Salaffi F, Carotti M, Stancati A, et al. 2005 Health-related quality of life in older adults with symptomatic hip and knee osteoarthritis: a comparison with matched healthy controls. Aging Clin Exp Res 17:255–263. [PubMed: 16285189]
3. Li X, Majumdar S. 2013 Quantitative MRI of articular cartilage and its clinical applications. J Magn Reson Imaging 38:991–1008. [PubMed: 24115571]
4. Emrani PS, Katz JN, Kessler CL, et al. 2008 Joint space narrowing and Kellgren-Lawrence progression in knee osteoarthritis: an analytic literature synthesis. Osteoarthritis Cartilage 16:873–882. [PubMed: 18280757]
5. Kellgren JH, Lawrence JS. 1957 Radiological assessment of osteoarthrosis. Ann Rheum Dis 16:494–502. [PubMed: 13498604]
6. Gold GE, Cicuttini F, Crema MD, et al. 2015 OARSI Clinical Trials recommendations: hip imaging in clinical trials in osteoarthritis. Osteoarthritis Cartilage 23:716–731. [PubMed: 25952344]
7. Lee S, Nardo L, Kumar D, et al. 2015 Scoring hip osteoarthritis with MRI (SHOMRI): a whole joint osteoarthritis evaluation system. J Magn Reson Imaging 41:1549–1557. [PubMed: 25139720]
8. Nieminen MT, Rieppo J, Toyras J, et al. 2001 T_2 relaxation reveals spatial collagen architecture in articular cartilage: a comparative quantitative MRI and polarized light microscopic study. Magn Reson Med 46:487–493. [PubMed: 11550240]
9. Akella SV, Regatte RR, Wheaton AJ, et al. 2004 Reduction of residual dipolar interaction in cartilage by spin-lock technique. Magn Reson Med 52:1103–1109. [PubMed: 15508163]
10. Li X, Cheng J, Lin K, et al. 2011 Quantitative MRI using T1rho and T_2 in human osteoarthritic cartilage specimens: correlation with biochemical measurements and histology. Magn Reson Imaging 29:324–334. [PubMed: 21130590]
11. Wyatt C, Kumar D, Subburaj K, et al. 2015 Cartilage T1rho and T_2 relaxation times in patients with mild-to-moderate radiographic hip osteoarthritis. Arthritis Rheumatol 67: 1548–1556. [PubMed: 25779656]
12. Gallo MC, Wyatt C, Pedoia V, et al. 2016 T1rho and T_2 relaxation times are associated with progression of hip osteoarthritis. Osteoarthritis Cartilage 24:1399–1407. [PubMed: 26973330]
13. Neogi T 2012 Clinical significance of bone changes in osteoarthritis. Ed. Bianchi Gerolamo. Ther Adv Musculoskelet Dis 4:259–267. [PubMed: 22859925]
14. Radin EL, Rose RM. 1986 Role of subchondral bone in the initiation and progression of cartilage damage. Clin Orthop Relate Res 213:34–40.
15. Doherty M, Courtney P, Doherty S, et al. 2008 Nonspherical femoral head shape (pistol grip deformity), neck shaft angle, and risk of hip osteoarthritis: a case-control study. Arthritis Rheum 58:3172–3182. [PubMed: 18821698]
16. Cootes TF, Taylor CJ, Cooper DH, et al. 1995 Active shape models—their training and application. Comput Vis Image Underst 61:38–59.
17. Sarkalkan N, Weinans H, Zadpoor AA. 2014 Statistical shape and appearance models of bones. Bone 60:129–140. [PubMed: 24334169]

18. Waarsing JH, Rozendaal RM, Verhaar JA, et al. 2010 A statistical model of shape and density of the proximal femur in relation to radiological and clinical OA of the hip. Osteoarthritis Cartilage 18:787–794. [PubMed: 20171297]
19. Nelson AE, Liu F, Lynch JA, et al. 2014 Association of incident symptomatic hip osteoarthritis with differences in hip shape by active shape modeling: the Johnston County Osteoarthritis Project. Arthritis Care Res (Hoboken) 66: 74–81. [PubMed: 23926053]
20. Wise BL, Kritikos L, Lynch JA, et al. 2014 Proximal femur shape differs between subjects with lateral and medial knee osteoarthritis and controls: the osteoarthritis initiative. Osteoarthritis Cartilage 22:2067–2073. [PubMed: 25194496]
21. Hunter D, Nevitt M, Lynch J, et al. 2016 Longitudinal validation of periarticular bone area and 3D shape as biomarkers for knee OA progression? Data from the FNIH OA Biomarkers Consortium. Ann Rheum Dis 75:1607–1614. [PubMed: 26483253]
22. Bredbenner TL, Eliason TD, Potter RS, et al. 2010 Statistical shape modeling describes variation in tibia and femur surface geometry between control and incidence groups from the osteoarthritis initiative database. J Biomech 43: 1780–1786. [PubMed: 20227696]
23. Neogi T, Bowes MA, Niu J, et al. 2013 Magnetic resonance imaging-based three-dimensional bone shape of the knee predicts onset of knee osteoarthritis: data from the osteoarthritis initiative. Arthritis Rheum 65:2048–2058. [PubMed: 23650083]
24. Chan EF, Farnsworth CL, Koziol JA, et al. 2013 Statistical shape modeling of proximal femoral shape deformities in Legg-Calve-Perthes disease and slipped capital femoral epiphysis. Osteoarthritis Cartilage 21:443–449. [PubMed: 23274103]
25. Pedoia V, Samaan MA, Inamdar G, et al. 2017 Study of the interactions between proximal femur 3d bone shape, cartilage health, and biomechanics in patients with hip osteoarthritis. J Orthop Res 36:330–341. [PubMed: 28688198]
26. Nilsdotter AK, Lohmander LS, Klassbo M, et al. 2003 Hip disability and osteoarthritis outcome score (HOOS)—validity and responsiveness in total hip replacement. BMC Musculoskelet Disord 4:10. [PubMed: 12777182]
27. Pedoia V, Li X, Su F, et al. 2016 Fully automatic analysis of the knee articular cartilage T1rho relaxation time using voxel-based relaxometry. J Magn Reson Imaging 43:970–980. [PubMed: 26443990]
28. Pedoia V, Lansdown DA, Zaid M, et al. 2015 Three-dimensional MRI-based statistical shape model and application to a cohort of knees with acute ACL injury. Osteoarthritis Cartilage 23:1695–1703. [PubMed: 26050865]
29. Pedoia V, Su F, Amano K, et al. 2017 Analysis of the articular cartilage T1rho and T2 relaxation times changes after ACL reconstruction in injured and contralateral knees and relationships with bone shape. J Orthop Res 35: 707–717. [PubMed: 27557479]
30. Subburaj K, Valentinitsch A, Dillon AB, et al. 2013 Regional variations in MR relaxation of hip joint cartilage in subjects with and without femoralacetabular impingement. Magn Reson Imaging 31:1129–1136. [PubMed: 23684960]
31. Gregory JS, Waarsing JH, Day J, et al. 2007 Early identification of radiographic osteoarthritis of the hip using an active shape model to quantify changes in bone morphometric features: can hip shape tell us anything about the progression of osteoarthritis? Arthritis Rheum 56: 3634–3643. [PubMed: 17968890]
32. Goldring SR. 2009 Role of bone in osteoarthritis pathogenesis. Med Clin North Am 93:25–35xv. [PubMed: 19059019]
33. van der Kraan PM, van den Berg WB. 2007 Osteophytes: relevance and biology. Osteoarthritis Cartilage 15:237–244. [PubMed: 17204437]
34. Wright D, Whyne C, Hardisty M, et al. 2011 Functional and anatomic orientation of the femoral head. Clin Orthop Relat Res 469:2583–2589. [PubMed: 21213086]
35. Brandt KD, Radin EL, Dieppe PA, et al. 2006 Yet more evidence that osteoarthritis is not a cartilage disease. Ann Rheum Dis 65:1261–1264. [PubMed: 16973787]
36. Cox LG, van Donkelaar CC, van Rietbergen B, et al. 2013 Alterations to the subchondral bone architecture during osteoarthritis: bone adaptation vs endochondral bone formation. Osteoarthritis Cartilage 21:331–338. [PubMed: 23142725]

37. Reikerås O, Høiseth A. 1982 Femoral neck angles in osteoarthritis of the hip. Acta Orthop Scand 53:781–784. [PubMed: 7136589]

38. Kitaoka HB, Weiner DS, Cook AJ, et al. 1989 Relationship between femoral anteversion and osteoarthritis of the hip. J Pediatr Orthop 9:396–404. [PubMed: 2732318]

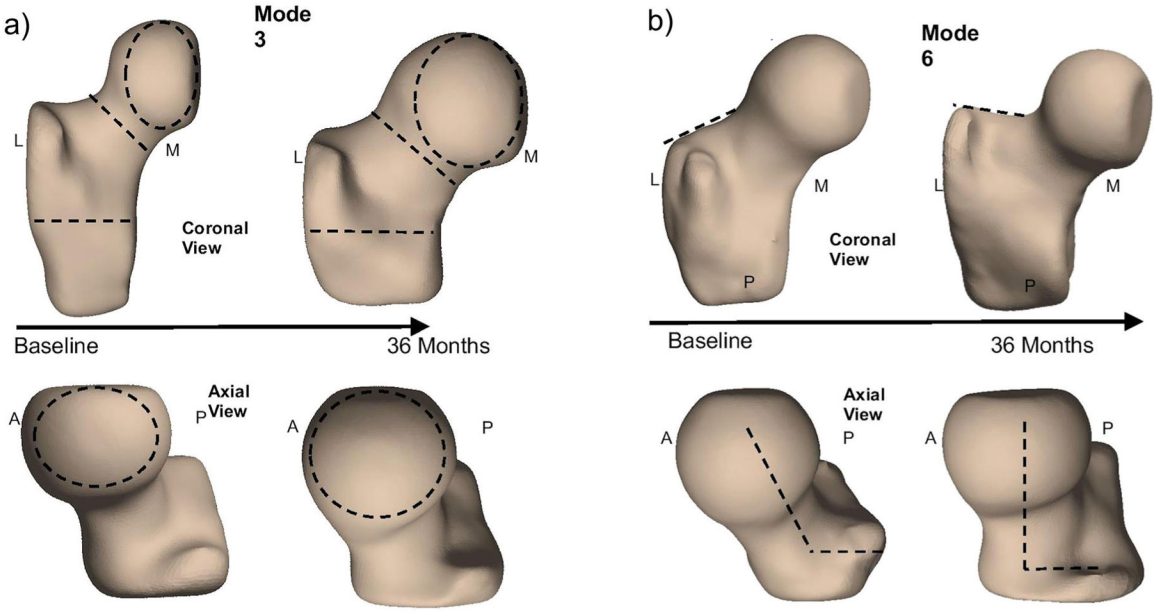

Figure 1.

Shape Mode 3 and Shape Mode 6 visualized at ±3 Standard Deviations (a) Shape change corresponding to change in Mode 3 values between the baseline and 36 months time point. At baseline the visualization of the change in Mode 3 is generated at −3 SD from the average while at 36 months the visualization is generated +3 SD from the mean mode values of the hips at that time point. At each time point the same image is shown in two different views. Dashed lines on the figures are added to draw the readers attention to changes in size of the femoral head, femoral neck, and femoral shaft between baseline and 36 months. Changes in Mode 3 values were seen to relate to the volume of the femoral neck and the femoral head. Lower mode values were associated with a more volumous femoral neck and a more volumonus femoral head. (b) Shape change corresponding to change in Mode 6 values between the baseline and 36 months time point. At baseline the visualization of the change in Mode 6 is generated at −3 SD from the average while at 36 months the visualization is generated +3 SD from the mean mode values of the hips at that time point. At each time point the same image is shown in two different views. Dashed lines are included to draw the readers attention to changes in the angle of the femoral head and neck between baseline and 36 months. Mode 6 values were seen to relate to the angle of the femoral head in relationt to the femoral neck. Lower Mode 6 values corresponeded to a shape with the femoral head angled more posterior to the femoral neck while high mode values showed a femoral head that was angled more anteriorly to the femoral head.

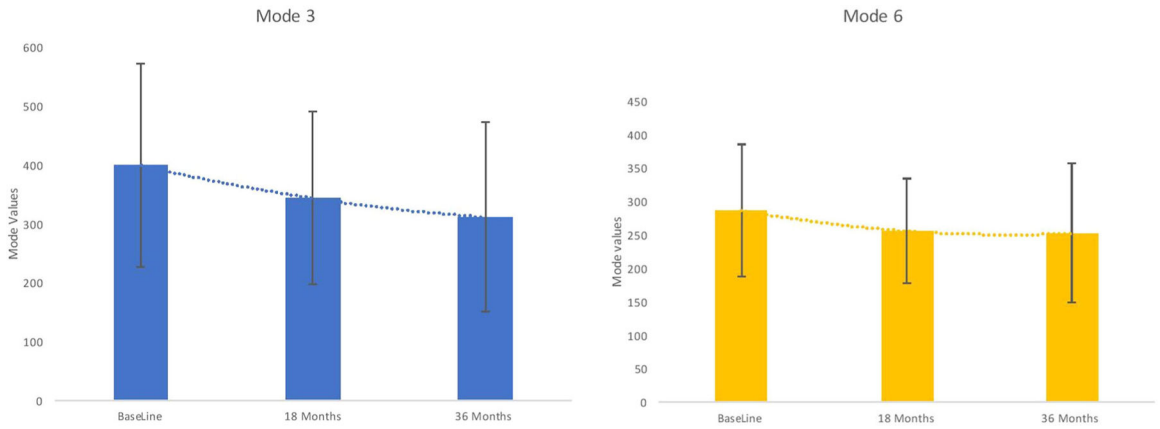

Figure 2.
Average Modes 3 and 6 values viewed at baseline,18 months, and 36 months.

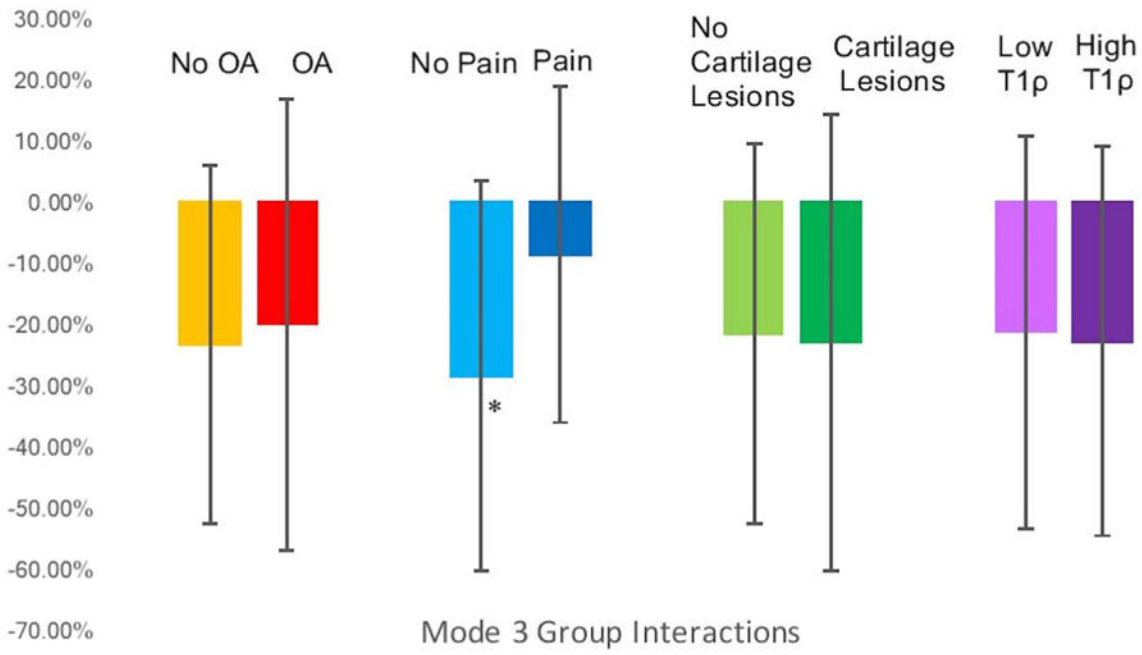

Figure 3.

Percent change between Mode 3 values at baseline and 36 months. The patients were split into groups based on various measures of osteoarthritis and joint health. These measures were KL scores (no OA vs. OA), HOOS pain scores (no pain vs. pain), SHOMRI scores (no cartilage lesions vs. cartilage lesions), and $T_{1\rho}$ values (low $T_{1\rho}$ vs. high $T_{1\rho}$). indicates significance.

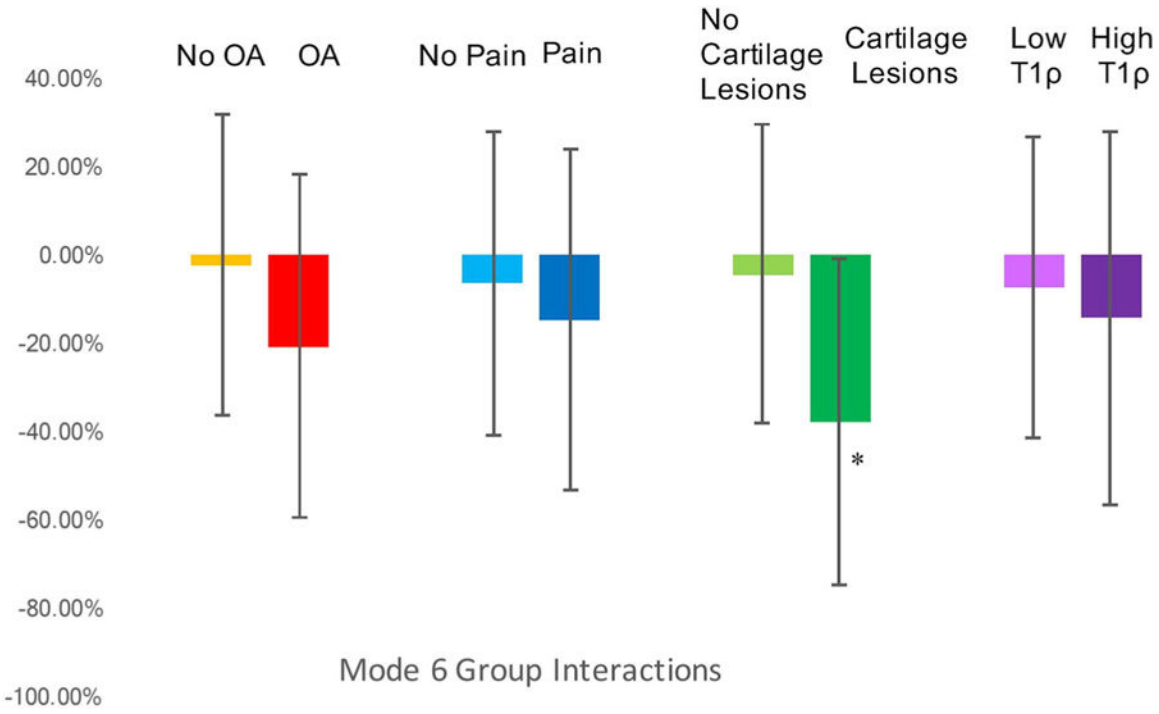

Figure 4.

Percent change between Mode 6 values at baseline and 36 months. The patients were split into groups based on various measures of osteoarthritis and joint health. These measures were KL scores (no OA vs. OA), HOOS pain scores (no pain vs. pain), SHOMRI scores (NO cartilage lesions vs. cartilage lesions), and $T_{1\rho}$ values (low $T_{1\rho}$ vs. high $T_{1\rho}$). indicates significance.

Table 1.

Patient Grouping by KL Scores, SHOMRI Scores, HOOS Scores, and $T_{1\rho}$ Values

Measure	Characteristics		Significance
SHOMRI (*N* = 46)	No cartilage lesions (*N* = 39, 84.78%)	Cartilage lesions (*N* = 7, 15.22%)	*T*-test
Age (years)	45.2 ± 12.47	61 ± 10.56	**0.006**
Gender (M:F)	19:27	6:1	0.04
BMI (kg/m^2)	23.4 ± 2.7	24.5 ± 1.8	0.21
Kellgren–Lawrence score (*N* = 45)	Low KL (*N* = 28, 62.22%)	High KL (*N* = 17, 37.78%)	*T*-test
Age (years)	44 ± 12.9	53.76 ± 12.3	**0.006**
Gender (M:F)	15:13	10:7	0.65
BMI (kg/m^2)	23.4 ± 2.7	23.9 ± 2.3	0.53
HOOS pain score (N = 46)	Low pain (*N* = 31, 67.39%)	Pain (N = 15, 32.61%)	*T*-test
Age (years)	47.7 ± 13.4	47.4 ± 13.8	0.943
Gender (M:F)	16:15	9:6	0.6
BMI (kg/m^2)	23.5 ± 2.10	23.8 ± 3.4	0.74
$T_{1\rho}$ values (N = 46)	Normal $T_{1\rho}$ (*N* = 33, 71.74%)	Elevated $T_{1\rho}$ (*N* = 13, 28.26%)	T-test
Age (years)	45.9 ± 12.8	51.8 ± 14.4	0.21
Gender (M:F)	17:16	8:5	0.55
BMI (kg/m^2)	23.0 ± 2.5	25.1 ± 1.9	**0.0049**

Patients with a SHOMRI score of greater than 1 in any compartment at any time point were classified in the Cartilage Lesion group. Patients with a KL score greater than 1 were classified in the High KL group. Patients with a HOOS pain score less than 90 at any time point were classified as the Pain group. Patients with $T_{1\rho}$ values above 2 standard deviations of the average $T_{1\rho}$ values at baseline in any compartment at any time were classified into the Elevated $T_{1\rho}$ group. Significant values at $p = 0.05$ are shown in bold.

Table 2.

Division of Patients Based KL Score and Grouping Based on Severity of OA

KL Score Group	Patients
No OA KL = 0	12
No OA KL = 1	17
Mild OA KL = 2	9
Moderate OA KL = 3	7

Patients with a KL score of 0 and 1 were group together and labeled as having no OA. Patients with KL of 2 were classified as having moderate OA and patients with KL of 3 were classified as having moderate OA.

Table 3.

Shape Modes Related to Time Without Including Demographics (Age, Gender, BMI)

			95% Wald Confidence Interval			
Mode #	**B**	**Std.Error**	**Lower**	**Upper**	**Wald Chi-Squared**	**Significance**
1	−0.269	0.9748	−2.18	1.642	0.076	0.783
2	1.414	0.7345	−0.026	2.853	3.704	0.054
3	**−2.441**	**0.3934**	**−3.212**	**−1.67**	**38.493**	**5.49E-10**
4	**1.398**	**0.5797**	0.262	**2.534**	**5.816**	**0.016**
5	0.049	0.4616	−0.855	0.954	0.011	0.915
6	**−0.947**	**0.3622**	**−1.657**	**−0.237**	**6.839**	**0.009**
7	0.164	0.3571	−0.535	0.864	0.212	0.645
8	−0.293	0.3873	−1.052	0.466	0.573	0.449
9	−0.43	0.3639	−1.144	0.283	1.397	0.237
10	**−0.418**	**0.2022**	**−0.815**	**−0.022**	**4.283**	**0.039**

Significant modes at $p = 0.05$ are bold.

Table 4.

Shape Modes Related to Time With Demographics Included (Age, Gender, BMI)

			95% Wald Confidence Interval			
Mode #	**B**	**Std. Error**	**Lower**	**Upper**	**Wald Chi-Squared**	**Significance**
1	3.325	27.4804	−50.536	57.186	0.015	0.904
2	27.004	33.5974	−38.846	92.853	0.646	0.422
3	2.004	24.7421	−46.49	50.498	0.007	0.935
4	8.937	21.1219	−32.461	50.336	0.179	0.672
5	2.422	15.3718	−27.706	32.55	0.025	0.875
6	**24.52**	**11.9581**	**1.083**	**47.958**	**4.205**	**0.04**
7	−12.311	13.8797	−39.515	14.893	0.787	0.375
8	−4.379	12.8841	−29.632	20.873	0.116	0.734
9	2.696	9.685	−16.286	21.678	0.077	0.781
10	10.963	8.0819	−4.877	26.803	1.84	0.175

Significant modes at $p = 0.05$ are in bold.

Table 5.

Mode 3 and Mode 6 Compared to KL, SHOMRI, HOOS, and $T_{1\rho}$ Values Over Time

			95% Wald Confidence Interval				
Mode #	**B**	**Standard Error**	**Lower**	**Upper**	**Wald Chi-Squared**	**df**	**Significance**
KL *time							
3	0.385	0.8564	−1.293	2.063	0.202	1	0.653
6	1.371	0.7944	−0.186	2.928	2.98	1	0.084
SHOMRI *time							
3	−0.302	0.8944	−2.055	1.451	0.114	1	0.735
6	2.083	0.9322	0.256	3.91	4.991	1	0.025
HOOS *time							
3	−1.959	0.8461	−3.653	−0.266	5.141	1	0.023
6	−0.059	0.805	−1.637	1.519	0.005	1	0.942
$T_{1\rho}$ *time							
3	−0.882	0.7604	−0.882	0.608	1.345	1	0.246
6	−0.25	0.8685	−1.952	1.452	0.083	1	0.774

B column indicates the unstandardized beta coefficient and demonstrates the change in mode values per unit of time.

Table 6.

Grouping of Progressors and Non-Progressors

Measure	Characteristics	Significance	Measure
SHOMRI progressors (N = 44 *)	Non-progressors (N = 22,50%)	Progressors (N = 22,50%)	T-test
Age (years)	47.08 ±14.11	48.18 ±14.11	0.76
Gender (M:F)	14:8	11:10	0.38
BMI (kg/m^2)	24.15 ± 2.18	23.02 ±2.87	0.11
$T_{1\rho}$ values	Non-progressors (N = 27,61.36%)	Progressors (N = 17,38.64%)	T-test
Age (years)	43.96 ± 12.88	53.28 ±12.46	0.019
Gender (M:F)	16:11	9:8	0.64
BMI (kg/m^2)	23.98 ± 2.41	23.03 ±2.77	0.243

* Two subjects were excluded as they did not possess the necessary demographic information.

Table 7.

ANCOVA Analysis of Mode 3 and Mode 6 Corrected With Age, Gender, and BMI

Mode	Type III Sum	df	Mean Square	*F*	Significance
SHOMRI progressors					
3	0.812	1	0.812	3.525	0.068#
6	0.487	1	0.487	2.112	0.154
$T_{1\rho}$ progressors					
3	0.799	1	0.799	3.932	0.055#
6	0.488	1	0.488	2.556	0.118

Borderline significant values are represented with a # ($p = 0.05 \pm 0.02$).