Research Article

Articular Cartilage Surface Roughness as an Imaging-Based Morphological Indicator of Osteoarthritis: A Preliminary Investigation of Osteoarthritis Initiative Subjects[1]

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Abstract

Current imaging-based morphometric indicators of osteoarthritis (OA) using whole-compartment mean cartilage thickness (MCT) and volume changes can be insensitive to mild degenerative changes of articular cartilage (AC) due to areas of adjacent thickening and thinning. The purpose of this preliminary study was to evaluate cartilage thickness-based surface roughness as a morphometric indicator of OA. 3D magnetic resonance imaging (MRI) datasets were collected from osteoarthritis initiative (OAI) subjects with Kellgren-Lawrence (KL) OA grades of 0, 2, and 4 (n=10/group). Femoral and tibial AC volumes were converted to two-dimensional thickness maps, and MCT, arithmetic surface roughness (S_a), and anatomically normalized S_a ($normS_a$) were calculated. Thickness maps enabled visualization of degenerative changes with increasing KL grade, including adjacent thinning and thickening on the femoral condyles. No significant differences were observed in MCT between KL grades. S_a was significantly higher in KL4 compared to KL0 and KL2 in the whole femur (KL0: 0.55±0.10mm, KL2: 0.53±0.09mm, KL4: 0.79±0.18mm), medial femoral condyle (KL0: 0.42±0.07mm, KL2: 0.48±0.07mm, KL4: 0.76±0.22mm), and medial tibial plateau (KL0: 0.42±0.07mm, KL2: 0.43±0.09mm, KL4: 0.68±0.27mm). $normS_a$ was significantly higher in KL4 compared to KL0 and KL2 in the whole femur (KL0: 0.22±0.02, KL2: 0.22±0.02, KL4: 0.30±0.03), medial condyle (KL0: 0.17±0.02, KL2: 0.20±0.03, KL4: 0.29±0.06), whole tibia (KL0: 0.34±0.04, KL2: 0.33±0.05, KL4: 0.48±0.11) and medial plateau (KL0: 0.23±0.03, KL2: 0.24±0.04, KL4: 0.40±0.10), and significantly higher in KL2 compared to KL0 in the medial femoral condyle. Surface roughness metrics were sensitive to degenerative morphologic changes, and may be useful in OA characterization and early diagnosis.

Introduction

Osteoarthritis (OA) is a prevalent degenerative condition most commonly affecting the knee, hip, ankle, and shoulder. While the pathomechanism of OA is not yet fully defined, several risk factors such as old age, joint trauma, obesity, ethnicity, sex, and genetic predisposition have been identified[1-3]. Although no successful long-term treatments are currently available, any potential intervention relies on accurate and timely diagnosis. Conventional x-ray radiography is currently considered the "gold standard" method of diagnosis, and the most common grading system to diagnose the severity of OA is the Kellgren & Lawrence (KL) score[4]. However, radiography can only detect secondary degenerative changes such as joint-space narrowing, bone sclerosis, osteophyte formation, and changes in gross bone morphology, and is unable to provide information about primary articular cartilage degeneration[4]. Furthermore, OA diagnosis on X-ray radiography is only possible after considerable degenerative changes have already taken place, and, to date, these changes are considered part of a self-accelerating and irreversible cascade.

Magnetic resonance imaging (MRI) is a powerful modality for the assessment of cartilage morphology. It provides excellent soft tissue contrast, enabling reliable evaluation of degenerative changes in the entire knee joint[4], and previous studies have demonstrated its superiority in diagnosing mild and moderate OA compared to conventional radiography[5-7]. Cartilage thickness and volume are frequently used to describe OA-induced morphological changes[8-10], and numerous studies have elucidated longitudinal and cross-sectional changes in thickness and volume between healthy and osteoarthritic patients[6; 11-14]. While overall joint space narrowing is considered the primary hallmark of OA, recent MRI-based studies have indicated that OA is not only associated with cartilage thinning[12; 15-17]. Using 3D MRI, Eckstein *et al.*[16] demonstrated that zones of both thickening and thinning are present on the femoral condyles in

subjects with KL grades 2 and 3, when followed longitudinally compared to baseline imaging. While they demonstrated an overall trend of articular cartilage thinning, 14% of patients exhibited thickening. Subcompartmental analysis in KL grade 2 knees showed medial tibiofemoral cartilage thickening to be as frequent as cartilage thinning.

In a quantitative analysis of thickness and volume, adjacent zones of cartilage thickening and thinning would numerically average, and this is a proposed rationale for the lack of a quantitative change in thickness or volume observed in mild and moderate OA. Reichenbach *et al.*[10] have demonstrated the ineffectiveness of using cartilage volume to distinguish between KL grade 0 and grade 2 knees, concluding that focal variations are missed by quantitative measures of whole-compartment thickness and volume. Sub-compartmental analyses afforded some additional sensitivity to these analyses[10], but come at the expense of information outside the volume-of-interest (VOI). Quantitative information aside from mean thickness which can provide a measure of the overall state of the cartilage surface may, therefore, prove beneficial in characterizing OA more sensitively. Recently, Maerz *et al.*[18] described and validated the use of surface roughness as a morphometric descriptor of cartilage degeneration in a rodent model of acute post-traumatic OA (PTOA). Mesh parameterization, a type of 3D-to-2D image processing transformation, was applied to convert 3D femoral and tibial cartilage volumes into 2D cartilage thickness maps for subsequent calculation of 2D surface roughness, representing the variation in cartilage thickness across the surface. The study demonstrated that while overall mean cartilage thickness changed by ~50%, surface roughness increased by over 250%[18].

More sensitive imaging-based morphological descriptors of articular cartilage can enable earlier and more sensitive OA diagnosis. To this end, the purpose of this study was to perform a proof of concept investigation on the use of mesh parameterization as an image processing

technique of clinical MRI data and the use of surface roughness as a morphological indicator of OA using clinical 3D MRI datasets from subjects of the Osteoarthritis Initiative (OAI) database.

Methods

Subjects and Magnetic Resonance Imaging

This study was conducted with full approval by an institutional review board. All patient and image data were obtained from the OAI, a large clinical database collected during a multi-center, longitudinal, prospective imaging study (https://oai.epi-ucsf.org). A preliminary pool of subjects from the progression cohort of the OAI was identified by querying the online OAI database based on a predefined set of exclusion and inclusion criteria. The OAI progression cohort is intended to study broad trends in the progression of OA and includes subjects with varying OA etiology and severity. Inclusion criteria were the availability of a baseline 3D double-echo steady state (DESS) MRI data set of the right knee upon enrollment, and availability of a baseline KL score as part of the provided clinical data from the OAI[19]. Exclusion criteria included a history of systemic testosterone, estrogen, gonadotropin-releasing hormone (GNRH), parathyroid hormone (PTH), or bisphosphonate use. Furthermore, subjects were excluded based on history of knee fracture, knee replacement surgery, and hyaluronic acid or steroid injection in the right knee. These inclusion and exclusion criteria were intended to identify a sample of subjects with OA and no medical or surgical history that may confound the assessment of knee cartilage morphology. Image data for all subjects who met the preliminary inclusion and exclusion criteria was requested from the OAI. The resulting pool of subjects underwent x-ray review by an orthopaedic surgery resident and any subjects with evidence of unreported knee replacement, ligament replacement (via identification of bone tunnels or implants), fracture

nonunion, or other anomalies were removed. From the remaining subjects, 10 subjects (5 men and 5 women) were randomly selected from KL grades 0, 2, and 4 using a computer algorithm. This final subpopulation of 30 subjects was included in the study. Demographic data was collected from the OAI database for each subject, including age, weight, and BMI. In the absence of an available visual analog pain score or equivalent measure of pain severity, the incidence of recurrent pain, defined as knee pain, soreness or stiffness more than half the days of a month in the past 12 months, was also collected to assess the proportion of patients in the sample population with symptomatic OA.

The MRI sequence used in this study was a sagittal 3D double echo steady-state (DESS) sequence acquired with a 3.0 Tesla (T) MRI system (Siemens Magnetom Trio, Erlangen, Germany) equipped with a quadrature transmit-receive knee coil (USA Instruments, Aurora, Ohio, USA). The resulting in-plane resolution of the sequence is 0.37 mm x 0.46 mm with a slice thickness of 0.7 mm. Full technical details and validation of the 3D DESS sequence can be found in previous OAI pilot studies[11; 20; 21].

Segmentation of Femoral and Tibial Articular Cartilage Volumes

Femoral and tibial cartilage volumes were segmented from each 3D MRI stack in a blinded fashion using MATLAB (Mathworks Inc., Natick, MA, USA). The MRI stack was resampled to 0.37 mm isotropic voxels and displayed in a custom multi-plane viewing interface, and a volume of interest (VOI) composed of articular cartilage, the bone-cartilage interface (BCI), and a thin layer of subchondral bone (excluding bone marrow) was manually outlined, as previously demonstrated for the isolation of articular cartilage[18; 22]. Briefly, a single author (KG) performed manual outlining of individual, spaced sagittal slices, and a morphing algorithm

(MATLAB File Exchange, http://www.mathworks.com/matlabcentral/fileexchange/61313-morph-binary-images) was used to interpolate the slices between manually-contoured slices to produce the 3D VOI. From this VOI, the final articular cartilage volume was then isolated via region growing (MATLAB File Exchange 2013, Christian Würslin, University of Tübingen, Germany). Quality control of all segmentations and final cartilage volumes was performed by the senior author (TM).

Thickness Map Generation via Mesh Parameterization

Cartilage thickness maps were computed for each sample based on a previously described and validated algorithm[18]. The overall process of mesh parameterization analysis is demonstrated in Figure 2. The BCI is isolated from the cartilage volume, triangulated into a mesh surface, and preprocessed to remove the "stair-step" associated with voxel data and ensure a smooth, congruent surface. The smoothed mesh is then mapped from the 3D to 2D using conformal mesh parameterization, designed to minimize spatial deformation. In this cohort the mean angular distortions of femoral and tibial parameterizations were 0.26 ± 0.04° and 0.06 ± 0.01°, respectively, and the mean areal distortions were 7 ± 3% and 1 ± 1%, respectively, indicating that the parameterization induced minimal spatial deformation (see supplemental information for additional numerical data regarding distortion, Table S1 and S2). This conformal mapping is used to build a 2D cartilage thickness map containing precise measurements of cartilage thickness normal to the BCI. Separate cartilage parameterizations were performed for the medial tibial plateau, lateral tibial plateau, and femur, and the femur was then subdivided into medial condyle, lateral condyle, and trochlear compartments by a single author (MDN) via a semi-automated algorithm. Using the whole femur parameterization and a 3D femur reconstruction as

an anatomical reference, points were selected on the medial edge of the medial condyle (localized as a deflection in the cartilage border, Figure 2C), intercondylar notch, and lateral border of the lateral condyle (a deflection in the cartilage border axially in-plane with the corresponding point on the medial condyle, Figure 3C). Lines were drawn between these points to divide the femur into compartments.

Quantitative Thickness Map Analysis

Mean cartilage thickness, areal arithmetic surface roughness (S_a), and normalized areal arithmetic surface roughness ($normS_a$) were computed for the whole femur and whole tibia as well as for the individual compartments of the femur and tibia. S_a is a standardized surface roughness metric defined by ISO 25178 and can be defined as the average deviation of a surface from its mean thickness, given by following equation:

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where t^{ij} is the thickness of the cartilage surface at point (i,j) and μ_t is the mean thickness of the surface. For individual compartments, the mean thickness of the compartment was used for S_a calculation. Traditional use of S_a in metrology is reported in absolute length units, as measurement of topographical deviations across a surface does not generally require normalization. However, in this study calculation of S_a is an assessment of changes in cartilage thickness, and thus calculation of S_a is subject to differences in native cartilage thickness between subjects due to anatomic variability. To anatomically normalize surface roughness, normS_a was calculated by dividing S_a by the mean cartilage thickness of the whole femur or whole tibia. The use of mean cartilage thickness was chosen as a means of normalization because other anatomic features able to be reliably obtained from a knee MRI (e.g. intercondylar distance) are at a much larger length-scale than articular cartilage (i.e. several centimeters vs single millimeters), and their use in normalization would skew data considerably.

Statistical Analysis

All statistical analyses were performed using SPSS (v22, IBM, Armonk, NY, USA). Normality and homogeneity of variances were assessed via Shapiro-Wilk and Levene's tests, respectively. Differences in demographics, mean cartilage thickness, S_a, and normS_a between subjects of KL grades 0, 2, and 4 were assessed using one-way analysis of variance (ANOVA). Multiple comparisons were performed using a Šidák post-hoc *t*-test. Variables that failed to meet the assumption of homogeneity of variances were analyzed via a Welch ANOVA and a Šidák

post-hoc *t*-test with unequal variances assumed. *P*-values less than 0.05 were considered significant.

Results

Demographic information about the final subject population is given in Table 1. There were no significant differences in age, weight, or BMI between KL grades. Pain incidences indicate that KL0 and KL2 subjects were largely asymptomatic populations, whereas KL4 subjects were more likely to exhibit recurrent knee pain.

Representative cartilage thickness maps of the femur and tibia demonstrate compartment- and subcompartment-dependent variations in cartilage thickness as a function of increasing KL grade (Figure 3). The final patient population included instances of both medial and lateral compartment degeneration, and representative AC thickness maps of KL4 subjects demonstrate the differential distribution of AC thickness in both forms of joint collapse (Figure 4). Femoral AC thickness maps of KL0 exhibits zones of natively thicker cartilage at the weight-bearing regions of the femoral condyles and the trochlea. KL2 femoral thickness maps exhibited very slight, global decreases in AC thickness, and a zone of AC thinning was observed at the anterior aspect the medial or lateral femoral condyle, though generally not both (Figure 3). In instances of medial compartment collapse, femoral AC thickness maps of KL4 exhibited zones of markedly increased AC thickness at the posterior aspects of the femoral condyles and a distinct zone of AC thinning at the anterior and central aspect of the medial femoral condyle (Figure 3). This phenomenon was less prevalent in instances of lateral joint collapse, but a distinct zone of marked AC thinning was observed at the anterolateral aspect of the lateral condyle (Figure 4). Quantitatively, there were no significant differences in mean cartilage thickness between KL0,

KL2, and KL4 in the whole femur or any femoral compartment (Figure 5A). There were, however, demonstrable quantitative differences in femoral S_a between varying KL grades. Whole-femur S_a was significantly higher in KL4 compared to both KL2 and KL0, and medial femoral condyle S_a was also significantly higher in KL4 compared to KL2 and KL0 (Figure 6A). Quantitative differences were more sensitively detected between KL grades when assessing normSa. Whole femur normS_a was significantly higher in KL4 compared to both KL2 and KL0, and medial femoral condyle normS_a was significantly higher in KL4 compared to KL2 and KL0, and also significantly higher in KL2 compared to KL0 (Figure 6C). No significant differences in S_a (Figure 6A) or normS_a (Figure 6C) were observed between KL grades in the lateral femur or trochlea. Complete tabulated numerical results are available in supplementary information (Tables S3, S4 and S5).

Tibial AC thickness maps demonstrate natively thick AC at the central, weight-bearing region of KL0 tibiae and progressive AC thinning in the collapsed compartment with increasing KL grade (Figure 3). Differential decreases in AC thickness as a function of the mode of joint collapse are evident in KL4 subjects (Figure 4). In both modes of joint degeneration, drastic AC thinning is observed at the outer periphery of the affected compartment (i.e. medial aspect of medial compartment and lateral aspect of lateral compartment) (Figure 4). Quantitatively, there were no differences in mean AC thickness between KL0, KL2, and KL4 in the whole tibia or the medial or lateral tibial plateau, though non-significant trends of decreased mean thickness were observed (Figure 5B). Medial tibial plateau S_a was significantly higher in KL4 compared to KL0, but no significant differences in S_a between KL grades in the whole tibia or the lateral tibial plateau were observed (Figure 6B). As in the femur, the assessment of normS_a was more sensitive to progressive tibial AC changes: whole-tibia normS_a was significantly higher in KL4

compared to both KL2 and KL0, and medial tibial plateau normS_a was significantly higher in KL4 compared to both KL2 and KL0 (Figure 6D).

Given the observed incidence of both medial and lateral joint collapse, a retrospective sub-analysis of subjects with medial and lateral joint collapse was performed. Subjects in KL2 and KL4 groups were assigned to either "medial OA" or "lateral OA" groups based on varus (medial) or valgus (lateral) angulation on A-P radiographs, determined by an orthopaedic surgery resident (JO). Medial OA was present in 3 KL2 subjects and 6 KL4 subjects, while lateral OA was present in 7 KL2 and 4 KL4 subjects. No notable differences were observed between medial OA and lateral OA groups within KL2 subjects (data not shown). Compared with lateral OA, medial OA was associated with significantly higher mean thickness of the whole femur, whole tibia, lateral condyle, and lateral tibial plateau (Table 2). Medial OA was also associated with significantly higher medial condyle S_a and normS_a and significantly higher S_a in the whole tibia and both tibial compartments (Table 2).

Discussion

Magnetic resonance imaging enables accurate assessment of articular cartilage morphology to characterize degenerative changes during OA progression. As recent literature has indicated that OA is not only associated with articular cartilage thinning but also with focal zones of thickening[12; 15-17], which may hinder the use of mean thickness or volume in characterizing cartilage degeneration in the setting of OA, the exploration of new metrics of degeneration is warranted. The purpose of this proof-of-concept study was to apply mesh parameterization as an image processing technique of clinical MRI data and to investigate the use of surface metrology parameters as morphometric indicators of OA. Our results demonstrate

that surface roughness is a sensitive parameter to detect changes in cartilage morphology associated with OA, while allowing analysis of the entire cartilage surface and volume. Surface roughness and normalized surface roughness provided a larger dynamic range between grades than mean thickness, which changed minimally, enabling a quantitative distinction of arthritic cartilage morphology. Furthermore, the creation of 2D cartilage thickness maps enables effective visualization of thickness variations across the entire cartilage surface.

Recent clinical studies have demonstrated that both cartilage thinning and thickening occur during the disease process[10; 12; 16; 17]. Our data corroborate these studies as thickness maps of femoral cartilage demonstrated adjacent zones of thick and thin cartilage, most notably on the medial femoral condyle of KL4 subjects with medial joint collapse (Figure 3, 4). Quantitatively, these two zones would numerically cancel, which is a proposed rationale for the insensitivity of whole-compartment cartilage thickness or volume as a morphological metric of OA[10]. However, since surface roughness calculates the mean surface deviation relative to a mean thickness, adjacent zones of thickening and thinning numerically increase rather than diminish surface roughness. This makes surface roughness particularly suited to characterization of whole-compartment changes. Both S_a and normS_a exhibited a greater dynamic range of measurement between KL grades in our study. Compared to KL0, mean thickness of KL4 knees were 3% greater in the whole femur, 2% lower in the medial femoral condyle, 16% lower in the whole tibia, and 13% lower in the medial tibial plateau condyle. In contrast, S_a in the same regions was 41%, 81%, 28% and 62% higher, respectively. In the medial femoral condyle, mean thickness of KL2 knees was only 1% lower than KL0, while S_a and normS_a were 14% and 19% greater, respectively. Compared to S_a, normS_a did not exhibit a greater dynamic range, but this anatomic

normalization resulted in decreased intragroup variance and, thus, more sensitive delineation of differences between KL grades.

A unique aspect of our analysis was the complete segmentation of the entire cartilage volume and analysis of whole compartments across both femoral and tibial surfaces, as opposed to analysis of predefined weight-bearing regions as commonly performed in other clinical characterizations of cartilage morphology[10; 12; 16; 23]. Consistent with previous characterizations of whole-cartilage thickness, we did not observe any changes in mean thickness between KL grades[10; 16]. This is likely due to a combination of factors, including the relatively small sample size of this proof-of-concept study (N=30, n=10), the combination of medial and lateral compartment collapse observed in our cohort, and the numerical cancellation of adjacent regions of thickening and thinning. Sub-compartmental changes in mean thickness with advancing OA have been demonstrated in previous studies[10; 14; 24; 25]. However, incorporation of information from the entire cartilage surface may enhance characterization of subtler/more diffuse changes to cartilage morphology, and thus the aim of the present study was to assess the efficacy of S_a and normS_a as metrics of whole-compartment cartilage changes. Future application of mean thickness and surface roughness to simultaneously characterize whole-compartment and sub-regional changes may enable earlier quantification of OA changes than currently possible. In addition, the geometric consistency of mesh parameterization mapping could enable future atlas-based sub-compartmental segmentation[26-28], improving repeatability and consistency.

In addition to facilitating the calculation of quantitative morphometric indicators of degeneration, the transformation of a 3D cartilage volume to a 2D thickness map via mesh parameterization enables visualization of the entire joint surface. The inherent 3D curvature of knee joint cartilage, particularly femoral cartilage, makes effective visualization difficult. As a

result, despite the high volume of literature studying cartilage morphology in OA, surprisingly few reports provide visual confirmation of numerical findings. Favre *et al*[29] and Cohen *et al*[30] report femoral cartilage thickness maps simply as isometric projections (or "snapshots") of 3D thickness maps. Dam *et al*[24] map medial tibial cartilage thickness within their region of interest to a 2D rectangular grid for visualization. Though the present study did not investigate any potential diagnostic benefit afforded by the ability to view the entire joint surface, future studies may focus on the utility of qualitative joint assessment based on the whole-joint thickness map. Since every discrete pixel of the thickness map originates from a point in 3D space within the raw MRI stack, accurate localization of a given feature from the thickness map (e.g. a zone of hypertrophic thickening) can be made within the MRI stack.

To our knowledge, this study is the first to utilize cartilage roughness, defined as variation in cartilage thickness, as an indicator of clinical cartilage degeneration, though other studies have employed different measures of surface metrology for cartilage characterization. Dam *et al*[25] employed a measure of surface roughness based on surface curvature to characterize clinical MRI data, finding a high correlation of roughness to radiographic OA. Previous studies have also correlated micro-level surface roughness patterns with cartilage degeneration via white light interferometry[31], histology[32; 33], and acrylic casting[34]. The assessment performed in these studies provides sensitivity to degenerative patterns such as delamination, fibrillation and fissure formation, as opposed to the macro-scale changes in cartilage thickness examined in this study. Favre *et al*[29] used 2D cross-sections of cartilage tissue to compute deviations in thickness profile between asymptomatic and OA, measuring significant alterations in KL2 and KL3 knees compared to asymptomatic patients. Despite the differences in roughness metrics employed in the present study and these others, our findings are in agreement with the concept that

metrology-based metrics could provide a useful tool to delineate the severity of degenerative pathology.

Both medial and lateral joint space narrowing are known to occur during the OA disease process, and both medial and lateral compartment collapse were observed in this cohort. Stratifying KL4 knees into “medial” and “lateral” OA subgroups, we observed some interesting differences (Table 2). Lateral OA is associated with significantly lower lateral cartilage thickness than medial OA, but there was not a corresponding difference in medial cartilage thickness. Whole femoral and tibial cartilage thickness is higher in subjects with medial OA compared to lateral OA. Medial OA is associated with significantly higher medial condyle S_a compared to lateral OA, but there was not a corresponding difference in lateral S_a – in fact lateral S_a was higher in the medial OA group than the lateral OA group. Collectively, these differences seem to reflect different mechanisms in these two subgroups. Ongoing studies are currently underway investigating potential indicators of these compartment-specific disease patterns.

This study should be interpreted in light of several limitations. This study is intended as proof-of-concept and is thus limited by its small sample size. As a preliminary investigation of the utility of mesh parameterization and surface roughness as generalizable indicators of whole-compartment cartilage changes in various grades of OA, irrespective of gender, etiology, mode of joint degeneration, or other stratifications, we limited our investigation to 30 randomly chosen subjects from the OAI without any further stratification. As such, absolute cartilage thickness and surface roughness numbers reflect the heterogeneity inherent in this cohort, and this was certainly a source of variance in our measurements. Future studies with larger sample sizes and appropriate subgroup stratification are necessary to obtain absolute, generalizable numbers, and may also demonstrate more sensitive detection of subtle morphologic changes. As with all

imaging-based studies, the accuracy of the presented analysis technique is fully dependent upon resolution and sufficient cartilage contrast with respect to surrounding tissues and fluids. It should be noted that the surface roughness patterns captured by our analysis are macro-scale patterns and do not capture microscopic changes such as cartilage fissures, fibrillations, or small lesions. It is generally assumed that a less congruent (more rough) cartilage surface should be associated with more advanced OA, and the results of this study and previous studies largely support this assumption[18; 25; 31-33]. However, it is important to note that this is ultimately still an assumption and that there may be certain cases in which roughness could decrease with increasing OA, particularly during sub-regional analysis. To calculate normS_a, anatomic normalization was performed to each subject's mean cartilage thickness – though we did not measure any significant difference in thickness between groups, any changes in thickness due to pathology could alter this calculation and future exploration of other means of anatomic normalization is warranted. A semi-automated cartilage segmentation involving manual determination of cartilage boundaries was employed in this study. More fully automated segmentation schemes in future studies could help to remove subjectivity and reduce labor time. We did not obtain any clinical data such as patient-reported outcomes, activity scores, or pain scores. Consequently, this study cannot draw any conclusions regarding the correlation of our calculated metrics to any clinical data. Delineation between degrees of OA in this study was done using the radiographic KL grade, which, despite its established clinical utility, has an inherently limited dynamic range and relies on indirect assessment of cartilage health via joint space narrowing and bony changes. This limited dynamic may have hindered the sensitivity of our metrics to degenerative changes.

Conclusion

This preliminary investigation assessed the use of mesh parameterization to facilitate calculation of surface roughness-based metrics on 3D MRI to quantitatively analyze varying degrees of radiographic OA. We found that whole-compartment S_a and normS_a were sensitive to morphologic differences in knees with KL0, and KL4 grade OA, and normS_a was furthermore sensitive to subtler morphologic differences between KL0 and KL2 grade OA. The ability to quantitatively distinguish between healthy and arthritic cartilage morphology holds substantial clinical utility, and future studies may assess the use of mesh parameterization and surface roughness in larger cohorts.

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Competing Interest Statement

The authors have no relevant conflicts of interest to disclose.

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Figure captions

Figure 1 – *Three-dimensional (3D) double echo stead-state (DESS) MRI utilized for the assessment of articular cartilage morphology. The data was acquired in sagittal orientation (A) and was reoriented into coronal (B) and axial (C) datasets for segmentation of articular cartilage. In-plane resolution: 0.37 mm x 0.46 mm. Slice thickness: 0.7 mm.*

Figure 2 – *Three-dimensional (3D) cartilage volumes were analyzed as follows: First, the bone-cartilage interface (BCI) was isolated from the overall cartilage volume (A), encompassing the medial, lateral and trochlear joint compartments on the femur (B) and the medial and lateral joint compartments on the tibia (not shown). The 3D BCI surface was mapped into the 2D domain via mesh parameterization (C) and this mapping is used to generate a two-dimensional (2D) cartilage thickness map describing thickness normal to the BCI (D).*

Figure 3 – *Representative A-P radiographs of subjects with Kellgren-Lawrence (KL) grade 0, 2, and 4 radiographic osteoarthritis (top), accompanied by corresponding femoral (middle) and tibial (bottom) cartilage thickness maps. Progressive medial compartment collapse is evident on A-P radiographs of KL2 and KL4, which corresponds to focal thinning of the medial femoral condyle and tibial plateau evident on cartilage thickness maps. Focal thickening is observed on the medial femoral condyles of KL4 and is directly adjacent to the zone of focal thinning. A subtle loss of tibial cartilage thickness is also evident with increasing KL grade.*

Figure 4 – *A-P radiographs (top) of subjects with Kellgren-Lawrence (KL) grade 4 osteoarthritis with corresponding femoral (middle) and tibial (bottom) cartilage thickness maps. A-P radiographs exhibit medial and lateral compartment collapse, corresponding to zones of*

focal cartilage thinning on the medial and lateral femoral condyles and tibial plateaux. Degenerate subjects in this dataset generally exhibited either medial or lateral compartment collapse but not both.

Figure 5 – *Mean cartilage thickness of the whole femur and individual femoral compartments (A), and whole tibia and individual tibial compartments (B). No significant differences in femoral mean thickness were observed between KL grades. Similarly, no significant differences in tibial mean thickness were observed, though general trends of decreasing tibial cartilage thickness with increasing KL grade can be observed. Horizontal lines represent mean values for each group. Tabulated numerical results are available in supplementary information (Table S3).*

Figure 6 – *Arithmetic surface roughness (S_a) of the whole femur and individual femoral compartments (A) and of the whole tibia and individual tibial compartments (B) demonstrate significant differences with progression of osteoarthritis. S_a is significantly higher in Kellgren-Lawrence (KL) grade 4 subjects compared to KL0 and KL2 in the whole femur and medial femoral condyle, as well as the medial tibial plateau. Anatomically normalized S_a ($normS_a$) of the femur (C) and tibia (D) demonstrates more significant distinctions between KL grades. $normS_a$ is significantly higher in KL4 compared to KL0 and KL2 in the whole femur, medial femoral condyle, whole tibia, and medial tibial plateau. In addition, $normS_a$ is significantly higher in KL2 compared to KL0 in the medial femoral condyle, demonstrating sensitivity to early osteoarthritic changes. Horizontal lines represent mean values for each group. Tabulated numerical results are available in supplementary information (Table S4, S5).*

Table 1 – *Study population demographics stratified by Kellgren-Lawrence (KL). All aggregate values are given as mean ± standard deviation (range).*

KL Grade	Age (years)	BMI	Weight (kg)	Pain Incidence*
0	56.5 ± 7.5 (50 - 70)	29.4 ± 4.7 (20.1 - 36.3)	84.8 ± 17.3 (55.1 - 119.1)	0/10 (0%)
2	64.2 ± 11.6 (46 - 77)	31.3 ± 4.2 (24.9 - 38.5)	84.1 ± 15.1 (66.8 - 111.5)	1/10 (10%)
4	61.8 ± 8.3 (53 - 77)	29.5 ± 5.7 (23.6 - 42.4)	85.2 ± 20.2 (61.2 - 120.6)	5/10 (50%)
Combined	60.8 ± 9.6 (46 - 77)	30.1 ± 4.8 (20.1 - 42.4)	84.7 ± 17.1 (55.1 - 120.6)	6/30 (20%)

**Pain incidence, as defined in Osteoarthritis Initiative data collection forms, refers to "right knee pain, aching or stiffness: more than half the days of a month over the past 12 months."*

Table 2 – *Sub-analysis of KL4 subjects in medial OA vs. lateral OA subgroups. Results are shown as mean ± standard deviation. P-values were computed using Student's t-test.*

			Medial OA	Lateral OA	P value
Mean Thickness (mm)	Femur	Whole	2.81 ± 0.27	2.28 ± 0.36	**0.03**
		Medial	2.13 ± 0.15	2.42 ± 0.53	0.233
		Lateral	2.92 ± 0.25	1.68 ± 0.23	**< 0.001**
		Troch	3.39 ± 0.54	2.69 ± 0.61	0.095
	Tibia	Whole	2.18 ± 0.18	1.63 ± 0.06	**< 0.001**
		Medial	1.57 ± 0.17	1.98 ± 0.40	0.051
		Lateral	2.91 ± 0.32	1.28 ± 0.34	**< 0.001**
S_a (mm)	Femur	Whole	0.86 ± 0.15	0.68 ± 0.19	0.125
		Medial	0.92 ± 0.11	0.53 ± 0.04	**< 0.001**
		Lateral	0.66 ± 0.11	0.55 ± 0.12	0.169
		Troch	0.65 ± 0.23	0.54 ± 0.16	0.463
	Tibia	Whole	0.95 ± 0.17	0.60 ± 0.25	**0.028**
		Medial	0.83 ± 0.22	0.46 ± 0.16	**0.022**
		Lateral	0.68 ± 0.15	0.45 ± 0.10	**0.028**
$normS_a$	Femur	Whole	0.30 ± 0.03	0.29 ± 0.04	0.625
		Medial	0.33 ± 0.04	0.23 ± 0.02	**0.003**
		Lateral	0.24 ± 0.04	0.24 ± 0.05	0.918
		Troch	0.23 ± 0.07	0.23 ± 0.04	0.878
	Tibia	Whole	0.43 ± 0.06	0.36 ± 0.14	0.303
		Medial	0.38 ± 0.09	0.28 ± 0.09	0.123
		Lateral	0.31 ± 0.06	0.28 ± 0.06	0.423

Graphical Abstract Text:

A custom algorithm was used to create two-dimensional articular cartilage thickness maps of patients from the Osteoarthritis Initiative. Thickness maps demonstrate significantly increased surface roughness as a function of increasing Kellgren-Lawrence (KL) osteoarthritis (OA) grade, particularly in the medial femoral condyle, though mean cartilage thickness was not found to differ significantly between KL grades. Surface roughness-based metrics have potential utility as morphological indicators of OA.