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Region of interest analysis: by selecting regions with denuded areas can we detect greater amounts of change?

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Summary

Introduction: Based on recent analyses, the measures of short-term responsiveness of magnetic resonance imaging (MRI) derived cartilage morphometry may not be as large as earlier studies had suggested. We examined if by selecting regions of interest with denuded cartilage, the remaining cartilage within this region of interest was susceptible to greater rates of cartilage loss.

Methods: Subjects included for this analysis are a subset of the approximately 4700 participants in the Osteoarthritis Initiative (OAI) Study. Bilateral radiographs and 3 T MRI (Siemens Trio) of the knees and clinical data are obtained at baseline and annually in all participants. Hundred and fifty subjects from the OAI progression subcohort all of whom had both frequent symptoms and, in the same knee, radiographic osteoarthritis (ROA defined as definite tibio-femoral osteophytes on X-ray) based on a screening reading done at the OAI clinics. One knee from each subject was selected for analysis. Using sagittal 3D DESSwe MR images from the baseline and 12-month follow-up visit, a segmentation algorithm was applied to the cartilage plates of the index knee to compute the cartilage volume, normalized cartilage volume (volume normalized to bone surface interface area), and percent denuded area (Total Cartilage Bone Interface area denuded of cartilage). Summary statistics of the changes (absolute and percentage) from baseline at 1 year and the standardized response mean (SRM), i.e., mean change divided by the standard deviation (SD) of that change were calculated. Analyses are stratified into three groups according to baseline assessment of denuded area: those with no denuded area in the region of interest at baseline, and then two groups (intermediate denuded area ($\leq$median) and severe ($\geq$median) denuded area) of equal sample size.

Results: On average the subjects were 60.9 years of age and obese with a mean body mass index (BMI) of 30.3 kg/m^2. For the combined central medial femur and tibia the mean volume change for the whole sample was -48.2 (SD 159.8) mm^3, which gives an SRM of -0.30. In the subsample of knees with no denuded area the SRM was -0.25, in the knees with intermediate denuded area the SRM was -0.30, and in knees with severe denuded area the SRM was -1.00. For normalized volume of the central medial femur in the subsample of knees with no denuded area the SRM was -0.22, in the knees with intermediate denuded area the SRM was -0.26, and in knees with severe denuded area ($n = 23$) the SRM was -0.71. The magnitude of the SRMs was generally smaller in participants with no denuded area. In contrast, the SRMs in participants with denuded area were larger.

Conclusion: By selecting participants with the presence of cartilage regions with denuded area the ability to demonstrate change in cartilage loss in that specific location is markedly improved compared to persons without a full thickness lesion in that cartilage plate. This option for screening during recruitment in clinical trials could facilitate the detection of participants at greater risk of subsequent cartilage loss.
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Key words: MRI, Cartilage, Denuded area.

Introduction

Osteoarthritis (OA) remains a complex condition whose etiology and pathobiology of progression is poorly understood, and a condition for which available effective therapeutic options are limited to symptomatic treatment. Development of therapies aimed at joint preservation in OA is constrained by the relatively slow progress of the condition, its heterogeneous clinical manifestations, the ideal to expose patients to an unknown drug for as short a period as possible and the current need for long-term follow-up to observe changes in structure.

It is hoped that new technologies may improve the assessment of early disease development, and progression, and could greatly facilitate measurement of structural outcomes in OA clinical trials. Foremost among the potential imaging

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techniques is magnetic resonance imaging (MRI), a sensitive non-invasive method for assessing joint morphology[1].

There is a significant body of supporting data on the longitudinal change in cartilage volume as a responsive primary endpoint to reflect OA progression[1]. It is further claimed that MR images offer a more sensitive measure of OA and its progression than X-ray[2]. Early longitudinal studies suggested that changes of cartilage volume of the order of -4% to -6% (SD of $\sim 5\%$) occur per annum in OA in most knee compartments followed for periods up to 3 years[1]. The annual changes in cartilage volume exceeded the precision errors and appeared to be associated with clinical symptoms as well as with time to knee arthroplasty[3,4]. Highlighting data from two of these prior studies the annualized data from Cicuttini *et al*[5] demonstrate that the medial femoral standardized response mean (SRM) is 0.50 and the medial tibial SRM is 0.4. The data from Pelletier *et al*[6] show the medial femoral SRM is 1.1 and the medial tibial SRM is 1.1 over 24 months. However, based on more recent analyses the responsiveness of MRI derived parameters may not be as good as earlier studies had suggested[7,8].

The more recent studies using similar cartilage quantification techniques demonstrate cartilage volume loss of about -1 to -3% per year[8−12]. The SRMs are essentially consistent between these studies with a maximum SRM of ~ 0.4. Like the prior studies the measurement variance was of similar magnitude to the rate of change. Thus, these more conservative recent estimates have important implications for planning of future clinical trials of disease modifying treatments for OA using MRI techniques.

Using these conservative estimates for power calculation, study designs based on large MRI progression series currently in the public domain require large sample sizes if one uses cartilage volume as the endpoint. It is obviously preferable to confidently design studies based on smaller sample sizes and/or shorter study durations, as this would reduce the resource implications for MRI based interventional studies.

Several studies have suggested that baseline clinical, biomarker, and imaging features are predictive of progression of cartilage loss in the medial compartment of the knee and could be used to provide greater study power by selecting a population at greater risk for more rapid progression. These include increased body mass index (BMI)[13], an increased level of type II collagen C-terminal degradation products detected in the urine (uCTX-II)[14], the presence of varus malalignment at the tibio-femoral joint[10,11,15], the presence on MRI of subchondral bone marrow lesions[16] or meniscal abnormalities[17]. If the more conservative estimates of progression are real it will become more important to identify populations within this at greatest risk for progression.

Prior studies have also suggested that the presence of semi-quantitative cartilage defects may predict subsequent cartilage volume change[18−20]. The objective of this analysis was to ascertain if by selecting regions of interest with presence of denuded cartilage measured quantitatively, the remaining cartilage within this region of interest was susceptible to greater rate of change in cartilage morphometry measures from baseline to 1 year in knees with OA from a subset of participants from the Osteoarthritis Initiative (OAI) progression subcohort.

Materials and methods

STUDY SAMPLE

Subjects included for this analysis are a subset of the 4796 participants participating in the OAI Study, which is an ongoing 4-year, multi-center, longitudinal, prospective observational cohort study, focusing primarily on knee OA. The study protocol, amendments, and informed consent documentation were reviewed and approved by the local institutional review boards. Data used in the preparation of this manuscript were obtained from the OAI database, which is available for public access at http://www.oai.ucsf.edu. The specific datasets used are clinical data set 0.1.1 and Image Release 0.B.1 and 1.B.1.

OAI consists of two subcohorts: a Progression subcohort, and an Incidence subcohort. Two different populations of subjects were recruited; 1389 patients with radiographic evidence and symptoms of knee OA at baseline were recruited into the Progression subcohort and another group with risk factors for the development of symptomatic knee OA was recruited to the Incidence subcohort. All of the participants for the present study were drawn from the Progression subcohort.

The inclusion criteria for the Progression subcohort of the OAI required that both of the following criteria must be present together in at least one knee at baseline:

1. Frequent knee symptoms, defined as pain, aching or stiffness on most days of a month during the past year,
2. Radiographic evidence of OA (ROA) defined as definite tibio-femoral osteophytes (OARSI atlas grade ≥ 1) on X-ray. Subjects with severe narrowing (OARSI grade 3 narrowing or bone on bone) in both knees were planned to be excluded. The grading of osteophytes and joint space narrowing (JSN) was done at each individual OAI enrollment center.

The participants consisted of the first substantive data release from the OAI progression subcohort. These were selected by OAI from participants who had complete baseline and 1 year MRI data in early 2006, with blocking for sex and center. This was a convenience sample of subjects. The ultimate selection of participants and radiographic results in this study are based upon central radiographic readings.

RADIOGRAPHIC ASSESSMENT

Bilateral posteroanterior (PA) views were obtained using a SynaFlexer™ frame (Synarc, Inc., San Francisco, CA) to position the subject's feet reproducibly[21]. Baseline and follow-up radiographs of the sample of 160 subjects were read independently by two study readers, one a bone and joint radiologist (PA), and the other a rheumatologist David J Hunter (DJH). Knee X-rays were read in a paired fashion, blinded to sequence. The two central readers (DJH and PA) ***separately*** evaluated the Kellgren & Lawrence grade (K−L) (0−4 scale)[22] as well as individual radiographic features[23], i.e., osteophytes and JSN on a 0−3 scale of each knee at both time points using the Osteoarthritis Research Society International (OARSI) atlas. For the K−L grade we used adjudicated readings that were arrived at by a consensus of both readers at a later reading session, with both readers and an adjudicator present. Disagreements on JSN were also adjudicated if the two readers disagreed.

SELECTION OF KNEE FOR ANALYSIS

Bilateral MRIs from 160 participants were provided by OAI but only one knee from 150 patients (one knee per subject) was identified for analysis. The rationale for reducing the sample from 160 to 150 was that the budget for processing the images was limited and in addition we wanted to optimize the use of subjects more likely to progress. The selection of the index knee for this analysis was based on the presence of both symptoms (frequent knee pain) and ROA in the same knee. One hundred patients had unilateral symptomatic ROA, and this knee was chosen for analysis, regardless of radiographic severity. For the remaining participants with bilateral symptomatic ROA one knee was selected, favoring the knee with moderate disease more likely to undergo disease progression (for further details on knee selection see prior publication[8]).

MRI SEQUENCE PARAMETERS

Images were acquired on a 3 T MRI scanner (Siemens Magnetom Trio, Erlangen, Germany) with a quadrature transmit−receive knee coil (USA Instruments, Aurora, OH). For the purposes of cartilage segmentation we used the sagittal 3D DESSwe images with a slice thickness of 0.7 mm, 16.3 ms Repetition time (TR), 4.7 ms Echo Time (TE), 25° Flip angle (FA), 160 slices, 140 mm Field of View (FOV); 384×307 matrix; in-plane resolution 0.37×0.46 mm (interpolated to an isotropic in-plane resolution of 0.37×0.37 mm), 185 Hz/pixel bandwidth, 0% phase oversampling, 10% slice oversampling, 80% phase resolution, 100% slice resolution, one average, elliptical filter on, asymmetric echo off, anterior/posterior phase encoding, fast gradient and fast radiofrequency (RF) options (acquisition time 10 min 23 s).

MRI POST PROCESSING

The cartilage segmentation was done using Double Echo Steady State (DESS) MRI sagittal sequences acquired by the OAI. The DESS sequence provides a complete high-resolution view of the knee cartilage tissue with

good contrast and separation between fluid, cartilage, meniscus and bony tissue. The segmentation was done by VirtualScopics analysis methods and proprietary software[24,25]. The cartilage segmentation software of one of the time points was based on a knowledge based 3D deformable model of the cartilage tissue that adjusts its boundaries automatically until it matches the underlying image cartilage tissue. Then those segmentations were supervised and errors were corrected by trained technicians using VirtualScopics software, and inspected by an expert musculoskeletal radiologist (ST). Once segmentation was completed in one of the time points, the second time point was segmented by tracking that segmentation into the second time point. Once it was tracked, the tracked segmentation was again supervised and segmentation error was corrected by trained technicians and the final segmentation supervised by an expert musculoskeletal radiologist. Image pairs were blinded to time point (baseline or 1 year).

After image segmentation, the following measures were analyzed in the regions depicted in Fig. 1:

1. Cartilage volume.
2. Normalized cartilage volume (volume normalized to bone surface interface area). The bone surface interface area is the area of the cartilage in contact with bone. The normalization was done by dividing the measured cartilage volume by the area of measured cartilage in contact with bone plus the area of full thickness defects (denuded area of bone). Because normal knee cartilage is a thin tissue with a large area, the normalized volume is an equivalent measurement of the cartilage thickness for cartilage areas with no full thickness defects. Full thickness defects will reduce the cartilage volume but they will not affect the intact cartilage area that is used to compute the normalized volume values.
3. Denuded area (Total Cartilage Bone Interface area denuded of cartilage). The denuded area is the area of bone where a full thickness cartilage defect is present (see Fig. 2).

A trimming algorithm that removes cartilage tissue outside of a 1 mm thick boundary region was used to reduce the variability in the definition of cartilage tissue (see Fig. 3). The trimming algorithm worked by doing a 3D rendering of the baseline segmentation of bone and cartilage tissue, and then doing a mathematical morphology dilatation operation on the bone tissue not-covered with cartilage or denuded areas. The dilated bone was used to estimate a 3D region that included 1.0 mm of boundary cartilage tissue. The new 3D region was used to remove the boundary tissue at the baseline and then the same region was used to remove the same amount in the follow-up observation. Because the trimmed algorithm only removed cartilage tissue, the definition of denuded areas was not affected by the trimming algorithm. The trimmed results are presented for each cartilage morphometry biomarker.

STATISTICAL ANALYSIS

The objective of this analysis was to assess, in subjects with knee OA, the rate of natural progression of the disease. The measures of rate of progression included the change and percent change from baseline to 1 year in the regular (non-normalized) cartilage volume, as well as change and percent change of normalized cartilage volume within regions of the knee stratified by extent of denuded surface area. Due to patients being observed at variable follow-up times at 1 year (the range of interval between baseline and 1 year follow-up visit was 335−546 days), changes from baseline were annualized assuming a linear trend over time.

To control for possible image analysis biases, image pairs were randomized in a 1:1 ratio using a block randomization scheme to two different paired image analysis scenarios: baseline supervised segmentation followed by a computer-based tracked segmentation of the 1 year follow-up (denoted by workflow A) or 1 year supervised segmentation followed by a computer-based tracked segmentation of the baseline MRI (denoted by workflow B). Due to differences in image analysis workflow, annual decreases in thickness and volume in workflow A were smaller than that in workflow B, suggesting that there is a systematic bias in estimating annual change.

We developed a statistical model to estimate such bias when calculating the annual change using the following formula:

$$\text{Annual rate of change}_i = a_i + b_i \times \text{Workflow}$$

where workflow A that is supervised segmentation at baseline is denoted as 1; workflow B that is tracked segmentation at baseline is denoted as −1.
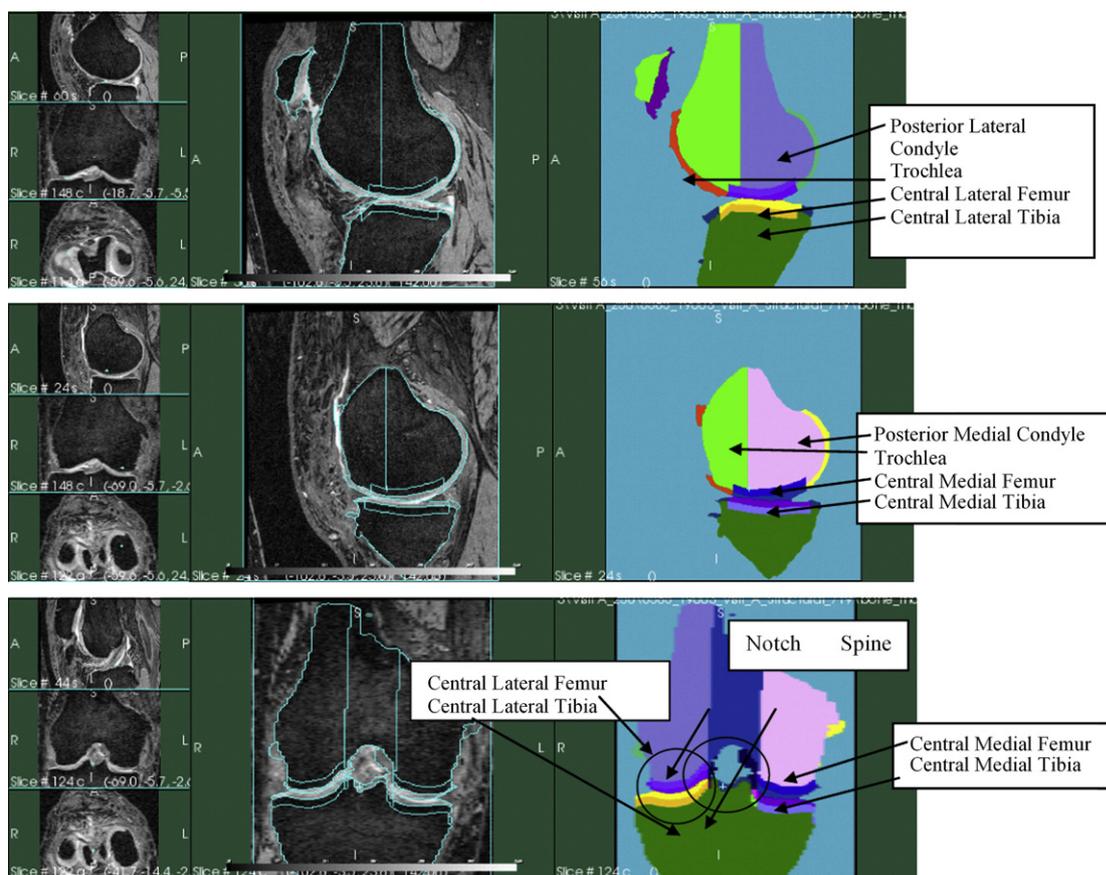

Fig. 1. MRI slices and schematics depicting cartilage regions. Top panel Lateral sagittal depiction of femoral and tibial regions. Middle panel. Medial sagittal depiction of femoral and tibial regions. Lower panel. Coronal depiction of femoral and tibial regions including notch and spine.
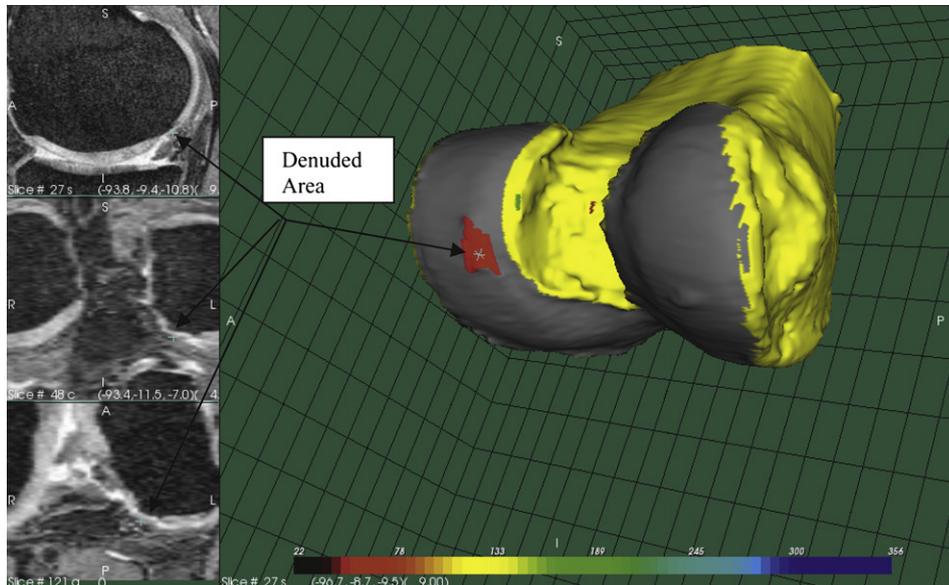
Fig. 2. Figure depicting denuded areas from a representative DESS image. The denuded areas are computed from the 3D rendering of the knee bones. The distal femur is displayed showing the denuded areas in red and the cartilage bone interface in grey (courtesy of VirtualScopics).
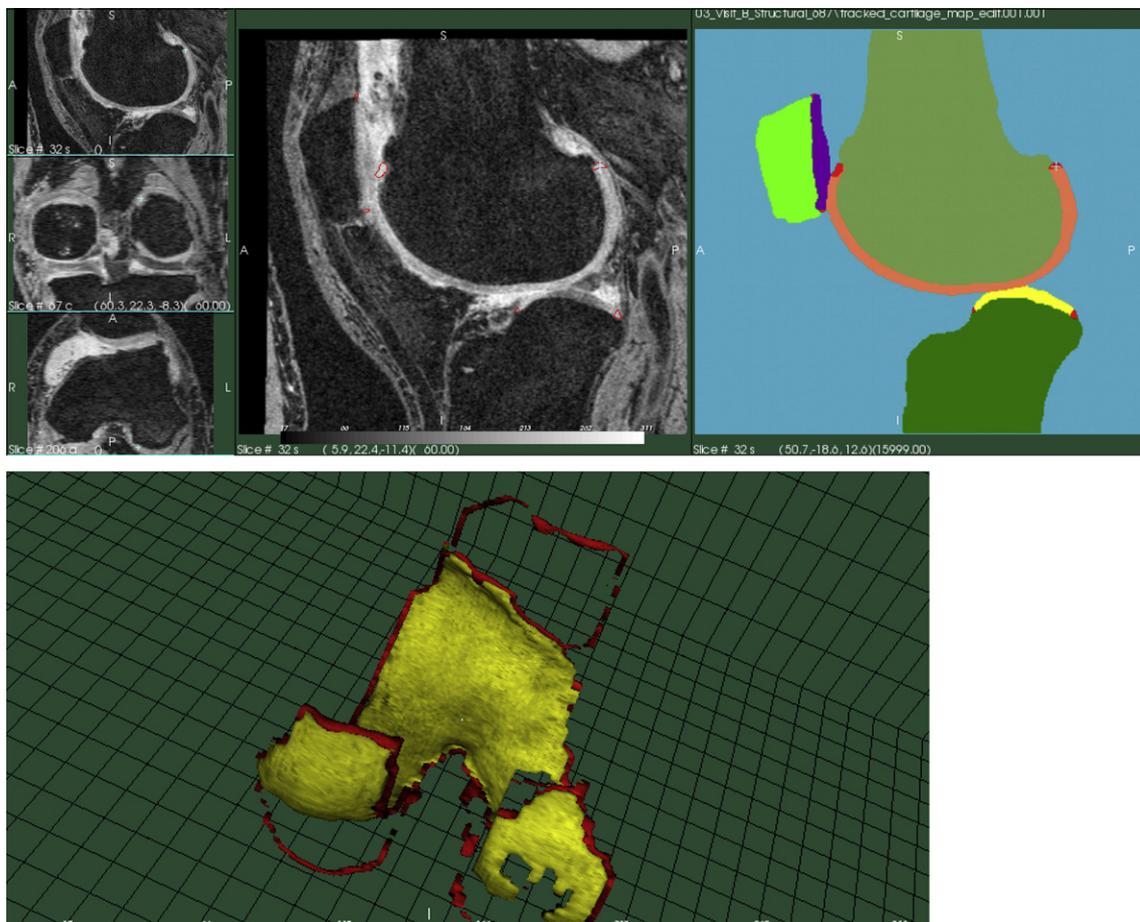

Fig. 3. Trimming. The computer automatically creates an edge template to consistently remove from both time points at most 1.0 mm from the edges of the cartilage tissue. Top, the red contours represent the cartilage tissue removed from the segmentation map. Bottom, 3D rendering of the removed tissue overplayed on top the 3D rendering of the femoral cartilage.

Therefore, the correct annual rate of progression is given by the a_i coefficient and the correction factor is the b_i coefficient. The b_i value is then used to correct all the observed values.

For each affected endpoint, the magnitude of bias, b_i, was estimated and used to obtain corrected (unbiased) measurements of change from baseline. These corrections were applied to the whole sample, and they rely on the reasonable assumption that the randomization was effective.

From the bias-corrected dataset, summary statistics of the changes (absolute and percentage) from baseline at 1 year and the SRM, i.e., mean change divided by the SD change were calculated. The baseline values, annualized mean change, and annualized percent change are each displayed. Analyses are stratified into three groups according to baseline assessment of denuded area: those with no denuded area in the region of interest at baseline, and then two groups (intermediate denuded area ($\leq$median) and severe denuded area ($>$median)) of equal sample size. The number of participants with denuded area was defined by cartilage plate and thus can differ between the cartilage plates. To compare the significance of the differences between the denuded area strata, we have used a one way analysis of variance (ANOVA) to test the difference in the annualized mean change of (normalized) cartilage volume trimmed among three groups of denuded surface area. Multiple comparisons with adjusted Tukey method were further performed. The denuded area variables were not normally distributed with a large number of values at both baseline and year one equal to zero. There were only 11 participants with denuded area in the posterior lateral femur so data from this region is not shown. All statistics were computed using SAS 9.0.

Results

On average the 150 subjects were 60.9 years of age and obese with a mean BMI of 30.3 kg/m^2. Approximately half (51%) of the study sample were female, as designed in the OAI protocol. Sixteen percent of the study sample did not have radiographic tibiofemoral (TF) OA using the commonly accepted criteria of K−L grade $\geq$2. This circumstance arose because eligibility into the OAI progression subcohort was based on the identification of a definite tibio-femoral osteophyte by the individual OAI enrollment center and some disagreement in radiographic assessment with the adjudicated scoring occurred. Further demographic characteristics are available in the original publication[8].

The prevalence and size of denuded area at baseline by anatomic region of the knee in these participants are displayed in Table I. At baseline denuded area lesions were more prevalent in the whole femur (47% of participants), central weight bearing portion of the medial femur (37%), and patella (39%).

The rate of natural progression of the disease as measured by the change in the regular (non-normalized) cartilage volume and normalized cartilage volume over a period of 1 year within regions of the knee is depicted in Tables II and III. The magnitude of change was further stratified by the extent of denuded surface area for each region. For example the

mean change in cartilage volume for whole sample ($N = 150$) for the central medial femur was -39.1 (SD 99.5) mm^3, which gives an SRM of -0.39. In the subsample of knees with no denuded area the SRM was -0.38, in the knees with intermediate denuded area ($n = 28$) the SRM was -0.33, and in knees with severe denuded area ($n = 27$) the SRM was -0.55. For normalized volume of the central medial femur in the subsample of knees with no denuded area the SRM was -0.33, in the knees with intermediate denuded area ($n = 28$) the SRM was -0.40, and in knees with severe denuded area ($n = 27$) the SRM was -0.54. For the combined central medial femur and tibia the mean volume change for the whole sample was -48.2 (SD 159.8) mm^3, which gives an SRM of -0.30. For cartilage volume of the subsample of knees with no denuded area the SRM was -0.25, in the knees with intermediate denuded area ($n = 24$) the SRM was -0.30, and in knees with severe denuded area ($n = 23$) the SRM was -1.00. For normalized volume of the central medial femur in the subsample of knees with no denuded area the SRM was -0.22, in the knees with intermediate denuded area ($n = 24$) the SRM was -0.26, and in knees with severe denuded area ($n = 23$) the SRM was -0.71. The magnitude of the SRMs varied across the different locations in the knee and was generally smaller in participants with no denuded surface area at baseline. In contrast the SRMs in participants with denuded area had SRMs of larger magnitude. The subsamples with the greatest responsiveness were those with severe denuded surface area in the combined central medial femur and tibia which had SRMs of -1.00 for cartilage volume and -0.71 for normalized cartilage volume. The predominant compartment affected by OA and the enrichment used for this subsample focused upon medial tibio-femoral OA. Somewhat surprisingly the SRMs for the severe denuded area sample for the central lateral tibia and central lateral femur also exceeded 0.7. Consistent with our initial hypothesis the SRMs increased from the no denuded surface area to the severe denuded area for the central medial femur and central medial tibia and their combination. In general the intermediate denuded surface area group showed intermediate values.

We performed further analyses (data not shown) to ascertain if it is worth combining the intermediate and severe denuded surface areas into one group. The SRMs in participants with any denuded areas were larger than those without denuded areas. For example the mean change of normalized cartilage volume trimmed was significantly different between two groups at lateral tibia ($P = 0.0173$), central lateral tibia ($P = 0.0005$) and central medial tibia ($P = 0.0044$). If the results for the SRMs were compared

Table I
Prevalence and size (%) of denuded area at baseline

Location	No. (%) of participants with denuded area at baseline	Size (%) of denuded area in intermediate group		Size (%) of denuded area in severe group	
		n	Mean (SD)	n	Mean (SD)
Femur	70 (46.7)	35	0.040 (0.019)	35	0.112 (0.040)
Lat Tibia	17 (11.3)	9	0.020 (0.009)	8	0.104 (0.113)
Med Tibia	35 (23.3)	18	0.119 (0.049)	17	0.454 (0.533)
Patella	59 (39.3)	30	0.050 (0.041)	29	1.172 (2.162)
Trochlea	53 (35.3)	27	0.043 (0.043)	26	0.344 (0.190)
Cent Lat Femur	16 (10.7)	8	0.015 (0.004)	8	0.109 (0.070)
Cent Lat Tibia	11 (7.3)	6	0.027 (0.010)	5	0.157 (0.184)
Cent Med Femur	55 (36.7)	28	0.068 (0.065)	27	1.057 (1.079)
Cent Med Tibia	38 (25.3)	19	0.156 (0.093)	19	0.878 (1.211)
Post Med Femur	20 (13.3)	10	0.031 (0.021)	10	0.160 (0.092)
c + p Med Femur	47 (31.3)	24	0.066 (0.052)	23	0.375 (0.196)
Cent Med F + T	47 (31.3)	24	0.112 (0.089)	23	0.842 (0.719)

Table II
Cartilage volume trimmed (mm^3): baseline value, annualized mean change and SRM for this change, annualized percent change, annualized mean change group by denuded surface area. N = 150

	Baseline mean (SD)	Mean change (SD) from model	SRM for mean change (95% CI)		Percent change (SD)	No denuded surface area				Intermediate denuded surface area				Severe denuded surface area			
						Mean change (SD)		SRM (95%CI)		Mean change (SD)		SRM (95%CI)		Mean change (SD)		SRM (95%CI)	
Femur	12031.9 (3224.0)	−19.7 (325.8)	−0.06	(−0.24, 0.10)	−0.12 (3.02)	33.1 (318.8)	0.10	(−0.13, 0.31)		−78.2 (357.4)	−0.22	(−0.61, 0.11)		−81.8 (295.1)	−0.28	(−0.70, 0.08)
Lat Tibia	2272.1 (733.0)	−18.7 (76.7)	−0.24	(−0.40, −0.09)	−0.98 (4.63)	−18.0 (74.5)	−0.24	(−0.41, −0.08)		−11.9 (103.1)	−0.12	(−1.25, 0.66)		−37.7 (89.7)	−0.42	(−1.78, 0.30)
Med Tibia*	1996.6 (642.6)	−6.5 (98.8)	−0.07	(−0.22, 0.09)	−0.28 (5.24)	1.9 (99.2)	0.02	(−0.17, 0.21)		−59.8 (106.3)	−0.56	(−1.43, −0.05)		−6.8 (71.5)	−0.10	(−0.63, 0.43)
Patella	2726.7 (1212.6)	−33.5 (134.3)	−0.23	(−0.42, −0.08)	−1.67 (7.48)	−18.5 (134.3)	−0.14	(−0.36, 0.07)		−64.2 (162.4)	−0.40	(−0.75, −0.06)		−49.5 (91.9)	−0.54	(−1.10, −0.16)
Trochlea	4571.7 (1473.8)	4.4 (193.6)	0.02	(−0.14, 0.18)	0.05 (4.68)	29.2 (204.7)	0.14	(−0.06, 0.37)		−35.7 (180.6)	−0.20	(−0.69, 0.20)		−46.7 (147.8)	−0.32	(−0.82, 0.10)
Cent Lat Femur	1751.7 (556.1)	−2.5 (63.6)	−0.04	(−0.21, 0.12)	−0.07 (3.75)	0.67 (64.3)	0.01	(−0.17, 0.18)		−13.1 (43.4)	−0.30	(−2.21, 0.45)		−44.4 (58.6)	−0.76	(−2.69, −0.18)
Cent Lat Tibia	1892.0 (608.6)	−16.5 (69.1)	−0.24	(−0.39, −0.09)	−1.12 (5.25)	−13.7 (68.2)	−0.20	(−0.36, −0.05)		−32.5 (75.9)	−0.43	(−3.43, 0.50)		−74.9 (71.3)	−1.05	(−3.61, −0.78)
Cent Med Femur	1509.5 (711.2)	−39.1 (99.5)	−0.39	(−0.53, −0.26)	−2.93 (9.75)	−40.6 (104.5)	−0.38	(−0.57, −0.23)		−35.5 (108.8)	−0.33	(−0.61, 0.005)		−37.3 (67.8)	−0.55	(−1.14, −0.15)
Cent Med Tibia	1320.9 (505.7)	−9.5 (82.5)	−0.12	(−0.26, 0.04)	−0.83 (7.26)	−0.52 (80.6)	−0.01	(−0.19, 0.18)		−44.4 (106.7)	−0.42	(−0.95, 0.01)		−27.2 (53.2)	−0.51	(−1.17, −0.06)
Post Med Femur	1741.9 (498.0)	−1.4 (76.3)	−0.02	(−0.19, 0.16)	0.12 (5.11)	−3.1 (76.6)	−0.04	(−0.22, 0.15)		29.4 (95.7)	0.31	(−0.36, 1.20)		−9.2 (42.5)	−0.22	(−1.18, 0.56)
c + p Med Femur	3251.3 (1103.8)	−40.01 (134.2)	−0.30	(−0.47, −0.13)	−1.18 (4.70)	−38.9 (134.2)	−0.29	(−0.47, −0.10)		−42.9 (155.5)	−0.28	(−0.71, 0.13)		−42.2 (112.3)	−0.37	(−0.97, 0.07)
Cent Med F + T	2830.3 (1183.0)	−48.2 (159.8)	−0.30	(−0.45, −0.15)	−1.99 (6.75)	−39.1 (158.8)	−0.25	(−0.43, −0.06)		−62.7 (212.0)	−0.30	(−0.63, 0.10)		−76.0 (76.3)	−1.00	(−1.68, −0.53)

*MT: Overall comparison, P-value is significant with $P = 0.0472$; no vs moderate denude area, $P = 0.0361$.

Table III

Normalized cartilage volume trimmed (mm): baseline value, annualized mean change and SRM for this change, annualized percent change, annualized mean change group by denuded surface area. N = 150

	Baseline mean (SD)	Mean change (SD) from model	SRM for mean change (95% CI)	Percent change (SD)	No denuded surface area Mean change (SD)	No denuded surface area SRM	Intermediate denuded surface area Mean change (SD)	Intermediate denuded surface area SRM	Severe denuded surface area Mean change (SD)	Severe denuded surface area SRM
Femur*	2.31 (0.36)	-0.005 (0.063)	-0.08 (-0.23, 0.08)	-0.19 (2.92)	0.008 (0.061)	0.13 (-0.09, 0.34)	-0.020 (0.072)	-0.28 (-0.62, 0.04)	-0.018 (0.054)	-0.33 (-0.75, 0.01)
Lat Tibia	2.26 (0.42)	-0.019 (0.081)	-0.23 (-0.39, -0.08)	-0.93 (4.66)	-0.020 (0.077)	-0.25 (-0.43, -0.09)	0.002 (0.099)	0.02 (-0.94, 0.85)	-0.033 (0.131)	-0.25 (-2.51, 0.46)
Med Tibia†	1.80 (0.37)	-0.007 (0.093)	-0.08 (-0.24, 0.08)	-0.46 (5.57)	0.003 (0.089)	0.03 (-0.16, 0.23)	-0.063 (0.114)	-0.55 (-1.29, -0.05)	-0.017 (0.081)	-0.21 (-0.70, 0.33)
Patella	2.28 (0.81)	-0.026 (0.111)	-0.20 (-0.39, -0.06)	-1.49 (7.65)	-0.022 (0.108)	-0.20 (-0.43, 0.01)	-0.028 (0.134)	-0.21 (-0.56, 0.19)	-0.034 (0.097)	-0.35 (-0.81, 0.01)
Trochlea	2.32 (0.55)	0.002 (0.093)	0.02 (-0.15, 0.18)	0.04 (4.54)	0.014 (0.093)	0.15 (-0.05, 0.37)	-0.010 (0.100)	-0.10 (-0.57, 0.31)	-0.028 (0.082)	-0.34 (-0.83, 0.06)
Cent Lat Femur‡	2.21 (0.41)	-0.003 (0.071)	-0.04 (-0.21, 0.12)	-0.20 (3.42)	0.001 (0.071)	0.02 (-0.16, 0.19)	-0.018 (0.063)	-0.28 (-1.43, 0.47)	-0.061 (0.064)	-0.96 (-2.70, -0.29)
Cent Lat Tibia	2.34 (0.49)	-0.019 (0.099)	-0.19 (-0.34, -0.03)	-1.01 (5.65)	-0.013 (0.089)	-0.15 (-0.30, 0.03)	-0.079 (0.211)	-0.37 (-1.48, 0.57)	-0.102 (0.128)	-0.80 (-4.20, -0.67)
Cent Med Femur	1.83 (0.71)	-0.044 (0.121)	-0.36 (-0.51, -0.23)	-2.82 (9.70)	-0.042 (0.127)	-0.33 (-0.51, -0.16)	-0.051 (0.129)	-0.40 (-0.67, -0.10)	-0.047 (0.088)	-0.54 (-1.09, -0.16)
Cent Med Tibia§	1.70 (0.45)	-0.013 (0.111)	-0.12 (-0.27, 0.04)	-1.03 (8.13)	0.002 (0.010)	0.02 (-0.17, 0.22)	-0.057 (0.144)	-0.40 (-1.04, 0.07)	-0.061 (0.136)	-0.45 (-0.86, -0.07)
Post Med Femur	2.34 (0.42)	-0.002 (0.101)	0.02 (-0.20, 0.14)	0.001 (4.67)	-0.005 (0.101)	-0.05 (-0.24, 0.13)	0.038 (0.120)	0.29 (-0.39, 1.19)	-0.001 (0.070)	-0.01 (-1.06, 0.70)
c+p Med Femur	4.17 (0.98)	-0.046 (0.164)	-0.28 (-0.45, -0.12)	-1.07 (4.34)	-0.041 (0.163)	-0.25 (-0.44, -0.06)	-0.063 (0.186)	-0.34 (-0.82, 0.05)	-0.048 (0.146)	-0.33 (-0.84, 0.14)
Cent Med F+T	3.54 (1.11)	-0.057 (0.203)	-0.28 (-0.43, -0.14)	-2.00 (7.32)	-0.041 (0.192)	-0.22 (-0.40, -0.03)	-0.068 (0.262)	-0.26 (-0.60, 0.15)	-0.124 (0.175)	-0.71 (-1.34, -0.46)

*F: overall comparison, P-value is significant P = 0.0328; no vs moderate denude area, P = 0.0692.
†MT: overall comparison P = 0.0171; no vs moderate denude area, P = 0.0135.
‡cLF: overall comparison P = 0.0425; no vs severe denude area, P = 0.0393.
§cMT: overall comparison P = 0.0124; no vs moderate denude area, P = 0.0752; no vs severe denude area, P = 0.0521.

with those in Tables II and III there does appear to be higher SRMs in the severe denuded surface area group compared to the composite group of intermediate and severe. Thus we continued the focus of presenting the intermediate and severe as distinct groups. We also examined the relation of denuded area in the adjacent plate and the effect of cartilage loss in the plate adjacent. For example if lateral tibial plate has denuded area the plate adjacent (lateral femur) is also at greater risk for cartilage loss. In general the magnitude of these changes in the adjacent plate was not as great as those in the local plate (site-specific) when a denuded area was present.

We also examined whether age and BMI was related to the presence of denuded area. Those with denuded area were generally somewhat older than those without denuded area (Table IV). However, BMI does not appear to be related to the presence of denuded area.

Discussion

Efforts are being made to enhance identification of participants with knee OA most likely to progress in clinical trials. This study demonstrates that by selecting participants and regions with the presence of a full thickness cartilage defect (denuded area) the ability to demonstrate change in cartilage loss in that plate is improved. Using this option for screening during recruitment in clinical trials could facilitate the detection of participants at greater risk of subsequent cartilage loss. Consistent with prior studies[8,10,12,26] the individual region with the largest magnitude of change appears to be the central medial femur. The combined cartilage volumes of the central medial femur and central medial tibia in the subsample with severe denuded area provided the most responsiveness.

These findings of cartilage loss occurring in regions with already denuded area are consistent with theories that suggest full thickness loss may be the first measurable change in morphometry rather than diffuse thinning[27]. In early OA cartilage may not be thin but rather thicker and swollen with water, which is imbibed by cartilage when the collagen network is disrupted and the role of proteoglycans is altered[28–31]. Previous studies have suggested that the initial pathology includes cartilage thickening, and it is not clearly understood if it represents an initial reversible phenomenon, permanent tissue damage or if it is the expression of a reparative process[32]. This may explain the lack of responsiveness of the traditional methods of measuring cartilage volume in large regions of the knee (e.g., medial tibia) and regional mean thickness as distinct from focal measures of change (region of interest analysis centered around focal defects[33]), as it is likely that large regions will encapsulate regions that are swollen. By focusing attention on smaller regions and those that already have a full thickness defect the opportunity to measure change is maximized. This is consistent with suggestions that cartilage defects measured semi-quantitatively may occur in early knee OA and precede cartilage volume loss[18,19].

Our own data from OAI showing conservative cartilage volume loss of about -1 to -3% per year[8] confirms findings in other studies including Mechanical Factors in Arthritis of the Knee (MAK)[10], Pfizer[26] and more recently data by Eckstein and colleagues from OAI[12]. These small rates of change have important implications for clinical trial planning of disease modifying treatments for OA using MRI techniques that could be enhanced by the results of this study. Whilst it is inherently appealing to identify participants at greatest risk for progression, this methodology would include acquisition and processing of an MRI during the screening process

Table IV
Relation of age and BMI to presence and absence of denuded areas

Location	Age in years			BMI (kg/m^2)		
	W/o denuded surface area	W/denuded surface area	*P*-value	W/o denuded surface area	W/denuded surface area	*P*-value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Femur	60 (9.7)	64 (9.8)	**0.0116**	30.7 (4.8)	29.9 (4.6)	0.3389
Lat Tibia	62 (9.9)	60 (10.2)	0.4604	30.2 (4.7)	31.1 (4.4)	0.4799
Med Tibia	61 (9.8)	66 (9.3)	**0.0044**	30.4 (5.0)	30.1 (3.6)	0.7570
Patella	61 (9.9)	64 (9.6)	**0.0391**	30.1 (4.6)	30.6 (4.8)	0.5083
Trochlea	62 (10.0)	62 (9.9)	0.5997	29.9 (4.6)	31.0 (4.8)	0.1954
Cent Lat Femur	62 (9.9)	63 (10.2)	0.6066	30.2 (4.4)	31.0 (7.0)	0.6613
Cent Lat Tibia	62 (10.0)	58 (8.6)	0.1849	30.3 (4.7)	30.0 (4.9)	0.8020
Cent Med Femur	60 (9.8)	65 (9.5)	**0.0105**	30.0 (4.7)	30.8 (4.7)	0.3082
Cent Med Tibia	61 (9.8)	66 (9.2)	**0.0046**	30.4 (5.0)	30.1 (3.9)	0.7499
Post Med Femur	61 (9.9)	65 (9.7)	0.0866	30.3 (4.8)	30.2 (3.9)	0.9262
c + p Med Femur	61 (10.0)	65 (9.1)	**0.0152**	30.2 (4.7)	30.6 (4.7)	0.5793
Cent Med F + T	60 (10.0)	65 (8.8)	**0.0055**	30.2 (4.7)	30.6 (4.7)	0.5640

with implications for participant burden and cost. If the central medial femur were chosen as the region of interest only 37% of the OAI progression cohort participants (based upon this subsample) will have a focal defect in this region with implicit impact on the screen failure rate. The upside is enhanced study efficiency and using a method with improved predictive value for detecting progression. As has been seen from prior studies there is marked heterogeneity in results of responsiveness for cartilage morphometry. This risk stratification method may also work when other cartilage segmentation techniques are used however, this needs to be formally assessed and these results replicated.

One caveat to this risk stratification methodology is that while one can identify knees with more rapid cartilage loss, it does not mean that these knees are optimal candidates for a clinical trial. If the pathological changes of cartilage loss are irreversible, and attention is focused on those at the end stage of the disease one may not be able to accomplish our goal of modifying the progress of the condition as a drug may not produce cartilage in the denuded area.

This study has several limitations. The automated, pairwise image segmentation process used imposes a bias on cartilage thickness and volume measurements, and is a unique feature of our methodology. Paired image analysis is typically more precise than unpaired image analysis, and biases imposed by these processes need to be presented and accounted for analysis. The relative advantages of our analysis methods will require independent segmentation and quantification of these images by alternative image analysis techniques.

The separation of the cartilage tissue into several compartments introduces noise into the region of interest measurements. Without this subdivision it is impossible to report localized changes and therefore the ability to detect changes will be minimized. On the other hand, the segmentation of cartilage plates was done using an automated process that only increases marginally the measurement error. The original description of the K−L grade was made and developed on weight bearing, fully extended films not on films acquired semi-flexed such as in this study.

In conclusion, this study demonstrates that by selecting participants with the presence of a severe full thickness cartilage lesions the ability to demonstrate change in cartilage loss in that specific location is markedly improved compared to persons without a full thickness lesion in that cartilage plate. This option for screening during recruitment in clinical trials could facilitate the detection of participants at greater risk of subsequent cartilage loss.

Conflict of interest

Acknowledgments

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