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Baseline cartilage thickness and meniscus extrusion predict longitudinal cartilage loss by quantitative MRI: data from the Osteoarthritis Initiative

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Abstract

Objective—To assess how meniscus damage and baseline cartilage thickness influence the rate of cartilage loss and knee pain.

Methods—Of 4,796 participants in the Osteoarthritis Initiative (OAI), 86 had baseline and 48 month follow-up quantitative MRI data for medial compartment cartilage thickness. Baseline meniscus pathology was scored by a musculoskeletal radiologist using Whole-Organ Magnetic Resonance Imaging Score (WORMS). Findings were correlated with 72-month Knee Injury and Osteoarthritis Outcome Score (KOOS).

Results—Univariate analysis showed cartilage change was not influenced by demographic variables. Multivariable regression revealed that initial cartilage thickness (−1.07 mm at 48 months for every 1 mm decrease at baseline, $p < 0.001$) and meniscus extrusion (−0.33 mm if present at baseline, $p < 0.001$) were the strongest predictors of medial compartment cartilage thickness at 48 months. KOOS pain scores did not correlate with cartilage loss.

Conclusions—Baseline cartilage thickness and meniscus extrusion are important and independent predictors for accelerated cartilage loss. However, the degree of cartilage loss did not correlate with mid-term change in clinical outcome scores.

Keywords

osteoarthritis; MRI; OAI; meniscus extrusion; cartilage

Introduction

Osteoarthritis (OA) is the most common form of joint disease, and now a leading form of disability in our increasingly active and aging population. The rate of total knee replacement (TKR) has more than doubled in the United States since 1999 particularly due to the lack of

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disease modifying OA drugs, expanded indications, an aging population, and an obesity epidemic [1]. By 2030, the demand is expected to increase to more than 3 million primary TKRs per year. [2] As such, the cost to our healthcare system will continue to grow exponentially.

The increasing incidence and cost has prompted many to investigate optimal ways to diagnose early, slow down progression, and treat this disease in a more effective manner. Joint space narrowing on standing AP radiographs and the use of the Kellgren-Lawrence (K-L) grading system are established methods for diagnosing and monitoring OA progression [3]. Recently, Riddle and Jiranek showed that worsening K-L grades were strongly associated with deteriorating function, increasing pain, and need for future arthroplasty [4]. However, a major limitation of conventional radiographs (and classification systems based on these radiographs) is its inability to identify early cartilage changes and to predict future cartilage loss and need for intervention [3,5].

As a result, alternative modalities have been sought to address these limitations. One of these modalities showing promising results is quantitative MRI (qMRI) given its ability in early OA to measure cartilage morphology and evaluate structural changes prior to their appearance on radiographs in early OA. In a nested case-control study, Eckstein et al was able to demonstrate that accelerated cartilage loss on qMRI was seen in knees going on to total knee replacement in the four years leading up to surgery[6]. Pelletier et al similarly noted qMRI's ability to predict accelerated cartilage loss and subsequent need for total knee replacement [7]. While these studies confirm an intuition that cartilage loss predicts future need for total knee arthroplasty, the relative importance of underlying factors contributing to progressive cartilage loss remains only partially defined.

The objective of this study, therefore, was to evaluate how demographic variables and meniscus damage influence the longitudinal extent of cartilage loss assessed by qMRI, and whether cartilage loss correlates with pain outcome scores. Improved understanding of the risk of OA progression conferred by these variables would better inform patient expectations, and could aid in identifying those with the most potential for therapeutic benefit during trials of disease modifying agents.

Materials and Methods

Study subjects

The Osteoarthritis Initiative (OAI) is a prospective, longitudinal, observational, and multicenter cohort study of men and women, ages 45-79, with or at increased risk to develop symptomatic and radiographic knee OA. These patients were enrolled at four different sites in the United States between 2005 and 2006. Participant inclusion and exclusion criteria as well as imaging and assessment protocols have been previously documented in studies based on the OAI database [8]. Patients within the database were followed with biannual evaluations that included questionnaires, physical exams, and different imaging studies. Our study is a retrospective analysis of data that was prospectively collected from the Osteoarthritis Initiative (OAI), which is available for public access at http://www.oai.ucsf.edu/. The specific data sets used for the project were V00WMTFMTH

(baseline) and V06WMTFMTH (48 month) for cartilage thickness data at baseline, and background/demographic data such as age, BMI, and gender from the P01 dataset. Knee Injury and Osteoarthritis Outcome Score (KOOS) outcomes measures (baseline and 72 months) data was also obtained from the KOOSKP (pain) and KOOSYM data sets. As this data is de-identified and publicly available, IRB approval was not required.

Of the 4,796 participants in the database, 86 subjects had baseline and 48 month quantitative MRI (qMRI) measurements reported for the medial femorotibial cartilage thickness (as of March 2014) and were included for our study. Exclusion criteria included subjects without qMRI data for the medial compartment.

Knee pain scores

While both the Western Ontario McMaster Universities Osteoartheritis Index (WOMAC) and Knee Injury and Osteoarthritis Outcome Score (KOOS) outcomes were available in the OAI data, we chose KOOS pain and symptom measures at baseline and 72 months for analysis of longitudinal changes in patient symptoms because the KOOS questionnaire included the full WOMAC index. Additionally, KOOS scores have been shown to be more responsive than the WOMAC scores [9]. The KOOS is a percentage score ranging from 0 to 100, with 0 indicating extreme problems, and 100 representing no problems.

MRI Analysis

The OAI utilizes 3T MRI across all sits. Cartilage thickness data was available as public dataset from the OAI; the reader is referred to previous publications regarding details of segmentation methodology used to generate these data [10, 11]. Briefly, cartilage segmentation was performed on a double oblique coronal 3D fast low angle shot (FLASH) MR sequence with water excitation, a slice thickness of 1.5 mm and an in plane resolution of 0.31 mm×0.31 mm; this segmentation was carried out at a central image analysis facility using proprietary technology (Chondrometrics GmbH, Ainring, Germany).

A single MSK radiologist (TS) generated Whole-Organ Magnetic Resonance Imaging Score (WORMS) scores and graded the degree of meniscal extrusion to evaluate meniscus pathology on baseline MRI's. For the WORMS meniscus score, the anterior horn, body segment, and posterior horn subsections were graded separately from 0 to 4, as described in Table 1. A cumulative grade for each meniscus was then determined using the scheme shown in Table 1, as described by Peterfy et al [12]; this algorithm was necessary to adjust for the non-linearity among the regional grades, which could lead to inconsistencies if the grades were simply summed.

We also generated a Meniscus Extrusion score, which was adapted from the WORMS scoring system, to evaluate the influence of meniscal extrusion on accelerated cartilage loss. The midposterior coronal slice where the medial tibial spine was of maximal volume on MRI was utilized to grade the degree of medial and lateral meniscal extrusion as 0=absent, 1= less than or equal to 50%, 2=greater than 50% meniscal extrusion. The point of reference for meniscal extrusion was determined as the tibial plateau osteochondral junction at the joint.

Statistics

Demographic data (age, BMI, and gender) were correlated with longitudinal quantitative cartilage loss via Pearson correlation and Student's t-test, respectively. The association between baseline morphological cartilage damage (as measured by WORMS scoring) and quantitative cartilage loss was compared using Spearman's correlation coefficient rho; morphological cartilage damage was also dichotomized (≤2 vs > 3) to increase statistical power of the comparison (t-test). Meniscus extrusion at baseline and subsequent cartilage loss was compared using the t-test. The association between KOOS scores and cartilage loss was assessed with Pearson's correlation. Multiple linear regression modeling with percent cartilage loss as outcome was performed; predictors were chosen *a priori* to include variables relating to meniscus injury (WORMS morphology score and extrusion), baseline cartilage thickness, and potential confounding demographic variables (age, gender, and BMI). Multivariable regression with KOOS pain and symptoms scores as outcome variables, and predictor variables as defined above in addition to 4-year cartilage loss was also performed.

Results

In our study cohort, the mean age was 59.9 (range 45-79), 48% were male, and mean BMI was 29.7 (range 18-46). Based on baseline and 48-month follow-up qMRI, the mean change in relative cartilage thickness over that interval was −7.0% of initial cartilage thickness (range: −42.6% to +8.3%), which was statistically significant based on a paired t-test analysis ($p < 0.0001$). On univariate analysis, relative cartilage change did not show any association with gender ($p=0.27$, unpaired t-test) and correlated poorly with age (Pearson $r = -0.24$) and BMI ($r = -0.18$).

Cartilage loss showed a weak but statistically significant correlation with increasing severity of meniscus damage as defined by the WORMS meniscus score (Spearman's rho = −0.23, $p = 0.03$), as seen in Fig 1. When WORMS data was dichotomized to less than or equal to 2 (n=44) and >3 (n=42), mean cartilage loss was statistically significant (−4.8% vs −9.2%, respectively; $p=0.05$, unpaired t-test).

Meniscus extrusion also positively correlated with future cartilage loss. Meniscus extrusion graded as absent (n=51), <50% (n=28), and >50% (n=7) correlated with unadjusted mean cartilage losses of −1.7%, −15.6%., and −10.7%, respectively ($p=0.0001$, Kruskal-Wallis). Higher relative cartilage loss in the intermediate extrusion group might be explained by the fact that those subjects with severe extrusion had thinner cartilage to begin with at baseline compared with absent and intermediate extrusion groups (3.01 vs 3.53 and 3.18 mm, respectively; $p = 0.01$, ANOVA). When extrusion was dichotomized, cartilage loss with medial meniscal extrusion present (n=35) was significantly greater (−14.6 ± 11.7%) compared to knees where meniscal extrusion was initially absent ($p < 0.0001$, unpaired t-test), as seen in Fig 2.

Univariate analysis showed that cartilage loss negatively correlated with the initial cartilage thickness (Pearson $r=-0.35$), as seen in Fig 3.

Multiple regression analysis was used to assess the extent to which demographic factors, meniscus damage, and baseline cartilage thickness predicted future cartilage thickness. We found that initial cartilage thickness and meniscus extrusion were the only significant predictors (Table 2); the model was significant ($p<0.0001$, adjusted $R^2= 0.89$). Using only these two variables in a regression model with relative change in cartilage thickness as the outcome, meniscal extrusion showed the largest magnitude of effect, leading to a 12% loss in cartilage thickness loss over the course of 4 years (95% CI: −0.15 to −0.08, $p <0.001$); in this simplified model, every 1 mm decrease in initial cartilage thickness resulted in −3.2% change in cartilage thickness at 4 years.

Interestingly, KOOS pain scores improved over the six year period following baseline MRI, from 65.5 (± 21.7) to 72.0 (± 19.6), $p = 0.02$ (paired t-test). There was no significant change in KOOS symptoms scores, from 73.6 (± 18.7) to 76.2 (± 19.0), $p = 0.27$. As expected, changes in KOOS pain scores correlated with changes in KOOS symptom scores ($r = 0.74$), but neither KOOS pain nor symptoms scores correlated with medial compartment cartilage loss ($r = −0.01$ and 0.09, respectively).

When change in KOOS pain and symptoms scores were used as the primary outcomes in multivariable regression analysis, there were no variables that showed a statistically significant correlation among predictors including age, sex, BMI, baseline cartilage thickness, meniscus damage (dichotomized), meniscus extrusion, and 4-year cartilage thickness loss; the overall model failed to reach significance ($p = 0.79$ and 0.86 for KOOS pain and symptoms, respectively). Change in KOOS pain scores did not correlate with change in cartilage thickness ($r = −0.01$), Fig 4. An example of one of the subject's baseline and 48-month MRI sequences demonstrating meniscal pathology, meniscus score, meniscal extrusion, articular cartilage loss, and KOOS score is shown in Fig 5.

Discussion

The interplay between the development of clinical osteoarthritis, imaging findings, and outcomes measures is complex. The aim of this study was to identify the extent to which basic demographic variables, meniscus injury, and baseline cartilage thickness affected the progression of osteoarthritis as measured by quantitative changes in cartilage thickness over a 4-year period, and knee pain over a 6-year period.

Before discussing the findings and their implications, it is important to note that the amount of cartilage loss observed in our study was consistent with the findings in previous literature[13]. Interestingly, the degree of cartilage loss was greater for more advanced stages of OA (K-L 3/4) as compared to early stages (K-L 1/2). Similar findings were found in Eckstein et al's work in which MRI-based cartilage thickness showed high rates of loss in knees with moderate and end-stage radiographic OA (by K-L) as compared to healthy or mild radiographic OA, which had a small rate of change indistinguishable from healthy knees[14]. Our results echo these from the literature by showing that thicker baseline cartilage is significantly associated with less cartilage loss as measured by qMRI. Therefore, qMRI evaluation of cartilage loss may be a better proxy for OA progression in later stages of OA, with alternative functional techniques such as T2 Mapping better suited for early

identification of cartilage at risk before the onset of morphological cartilage abnormalities and symptomatic OA[15]. In this vein, Lin et al showed that asymptomatic subjects scoring at either the high or low extremes of physical activity were more likely to exhibit progression of cartilage T2 changes over four years [16]. Such investigations might provide suitable targets for disease modifying agents or activity modifications earlier in the course of disease to reduce risk for OA progression.

The reproducibility of MRI measurements of cartilage thickness was previously reported as approximately 2% root mean square coefficient of variation [17]. As the observed mean thickness was approximately 3-4 mm in that study, the standard deviation of repeat measurements lies between 5-10%. In our study, many subjects exhibited only minor relative changes in cartilage thickness over the study duration, within these known reproducibility limits. However, it is also possible that some subjects who exhibited increases in cartilage thickness did so because of cartilage swelling, which has been postulated to occur in early OA and is observed in several animal OA models [17].

Our study revealed a trend toward male gender predisposition for subsequent cartilage loss, with an adjusted decrease of approximately −0.12 mm over 4 years compared to females, although this did not reach statistical significance. While female knee cartilage is actually thicker than males' when scaled to account for allometric differences[18], it is generally believed that females are at higher risk for developing osteoarthritis[19]. Interestingly, a subanalysis of our data revealed that 6/7 subjects who were scored as having severe meniscus extrusion were women. This fact aligns with recent observations that asymptomatic females exhibit relatively higher degrees of meniscus body extrusion than their male counterparts[20].

Recent literature has extensively studied the effect of meniscus pathology on the future development or progression of knee OA. For example, Raynauld et al studied the correlation between several patient variables and the loss of cartilage volume over two years[21]. Similar to our study, severe meniscal extrusion was found to be a significant risk factor for cartilage volume loss ($p=0.001$). However, they also found a statistically significant correlation between severe medial meniscus tear, bone marrow edema (BME), high BMI, and older patients, and an increased rate of cartilage volume loss ($p=0.005$, 0.03, <0.05, <0.05, respectively)[20]. Pelletier et al showed in their longitudinal study that severe meniscal extrusion, severe lateral meniscus tear, BME in the lateral compartment at baseline, and WOMAC pain change positively correlated with loss of cartilage volume on weight-bearing areas in knee OA patients assessed by qMRI[22]. These results were similar to those of Bloecher et al, who showed that decreased width of the medial joint space was highly associated with diminished meniscal coverage of the tibial plateau[23]. Badlani et al also found medial meniscus extrusion, complex tears, and tears with large radial involvement were more likely to develop radiographic signs of OA (K-L>2) compared to control[24]. Most recently, Driban et al examined a cohort from the OAI database and note accelerated knee OA in patients with MRI findings of medial meniscus pathology with extrusion and others with subchondral damage at baseline [25]. Similarly, OAI data showed that medial meniscus extrusion predicts a higher rate of incident radiographic knee OA, and that extrusion was more pronounced in those with earlier incident OA [26].

Our study also supports the importance of an intact meniscus on optimal load transmission and its ability to protect the native articular cartilage. When the ability of the meniscus to absorb and dissipate load through hoop stresses is compromised (for instance with partial or complete meniscal extrusion), more of the load is transmitted through the cartilage in reduced contact areas leading to increased wear and cartilage loss. Our study showed an adjusted estimate of −12% loss of cartilage thickness over the 4-year study period (after controlling for baseline cartilage thickness) when any meniscal extrusion was present at baseline.

Recent studies have shown a strong correlation between deteriorating imaging findings and outcome measures[6,27]. Rather than using need for joint replacement as a primary endpoint, outcomes measure like the KOOS and WOMAC scales have been used as proxies to evaluate the degree of disease as perceived by the patient. These questionnaires are validated for use in both short and long term assessment of pain, and it has been suggested that a change of 8-10 points in KOOS scores reflects the minimal perceptible clinical improvement[9]. Somewhat counterintuitive evidence that cartilage loss identified on radiographs and MRI correlates poorly with these outcome measures has recently emerged from the OAI data[28]; in fact, recent analysis of the OAI data has revealed that aggregate knee pain scores change little over similar six year periods[20]. In our smaller subset of subjects, we found that KOOS scores actually improved six years after baseline. This may be due in part to selection bias, as our inclusion criteria required longitudinal MRIs and subjects whose pain significantly worsened to the point of requiring knee arthroplasty would have been excluded. Regardless, evidence from our study further corroborates the idea that that cartilage loss, meniscus pathology, and other MRI findings *alone* are not uniformly responsible for driving symptomatology in osteoarthritis, and highlights the need to rely on patient symptoms in directing treatment and determining appropriateness of surgical intervention.

We acknowledge that our study has several limitations. One, the inclusion criteria (in addition to the criteria used for enrollment by the OAI at its inception) focused on subjects with baseline and 48-month qMRI data (in order to maximize the interval for qMRI), but only 86 out of nearly 5000 patients met that criteria. As a result of the sample size, we dichotomized both meniscus extrusion and the WORMS morphological score of meniscus damage in order to preserve statistical power. This study also did not include subregional analysis of the MRIs to assess cartilage loss, but rather relied on a more global measurement of the medial tibiofemoral cartilage. Previous studies have shown the central medial femorotibial compartment is the most sensitive MRI subregion for evaluation of cartilage loss[12,29,30]. Few subjects exhibited small positive changes in cartilage thickness over time, likely reflecting random error in measurement; the small magnitude of this error makes it unlikely to alter the conclusions of our study, which are based on larger patterns identified in this cohort.

In conclusion, our study identified baseline cartilage thickness and meniscus extrusion as the important and independent predictors for accelerated cartilage loss and development of worsening osteoarthritis. However, contrary to other reports in the literature, the degree of cartilage loss did not correlate with longer-term change in clinical outcome scores, which

highlights the complexity that drives OA symptomatology. Future studies should focus on better predictors of pain progression and worse outcome. T2 mapping and similar MRI techniques may assist with this process for identifying markers for future development of OA early on. From there, we can identify new disease modifying interventions that may slow the progression of OA and delay the need for total knee arthroplasty.

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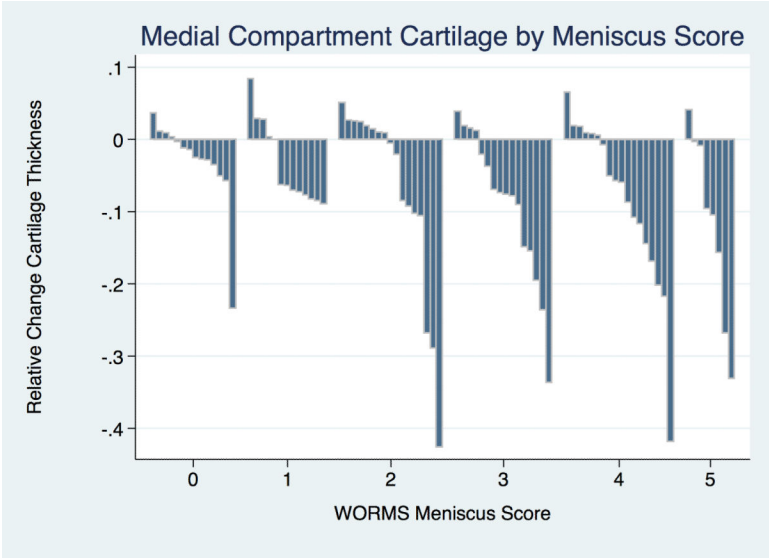

Fig. 1.

Waterfall plot showing individual subjects' longitudinal cartilage loss, grouped by WORMS (whole organ magnetic resonance scoring) meniscus score. With scores of 0-1, the magnitude of cartilage thickness changes were small except for one relative outlier. As baseline meniscus scores increase, reflecting more severe damage, subjects exhibit increasing magnitude of cartilage loss, with increasing frequency. Mean values are as follows: for WORMS score 0 (n=14): −3.1%; 1 (n=13): −3.6%; 2 (n=17): −7.2%; 3 (n=16): −9.0%; 4 (n=18): −8.4%; 5 (n=8): −11.6%. Many of the observed small changes in cartilage thickness are within the known range of reproducibility error for mean cartilage thickness measurements; apparent cartilage thickening could also be attributable to cartilage swelling, which has been posited to occur in early OA.

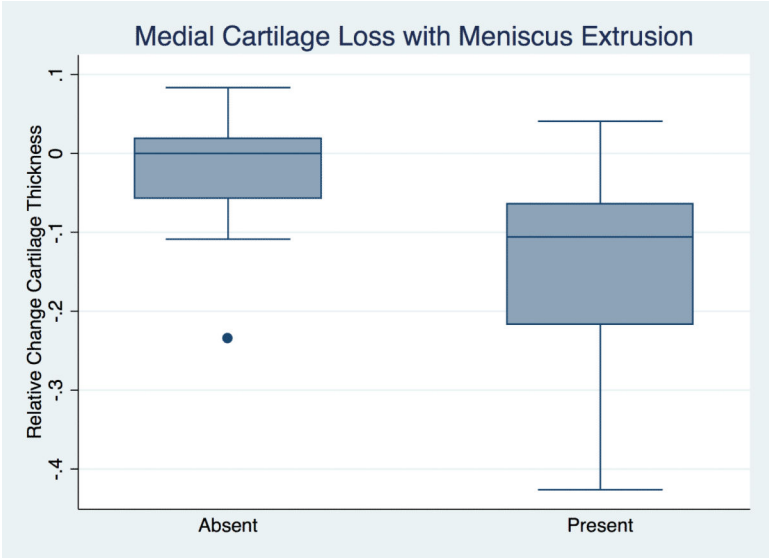

Fig. 2.

Box plot demonstrates that medial meniscus extrusion presence at baseline is associated with greater longitudinal cartilage loss in the medial tibiofemoral compartment, averaging −14.7% vs −1.7% ($p < 0.0001$) for subjects without extrusion. Each box defines the 75^{th} and 25^{th} percentiles, with median represented by the horizontal line within the box; upper whisker marks largest value ≤ upper quartile + 1.5*interquartile range; lower whisker marks lowest value ≥ lower quartile − 1.5*interquartile range. One outlier without meniscus extrusion demonstrated −23% relative change in cartilage thickness.

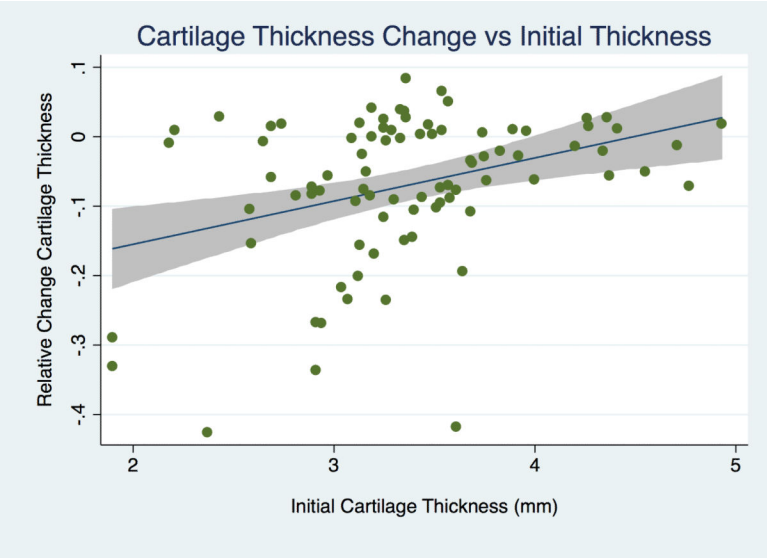

Fig. 3.

Linear regression (95% CI shaded gray) shows cartilage loss negatively correlates with baseline cartilage thickness (r = −0.35): thicker cartilage is itself protective against ensuing cartilage thinning (also, see Table 2).

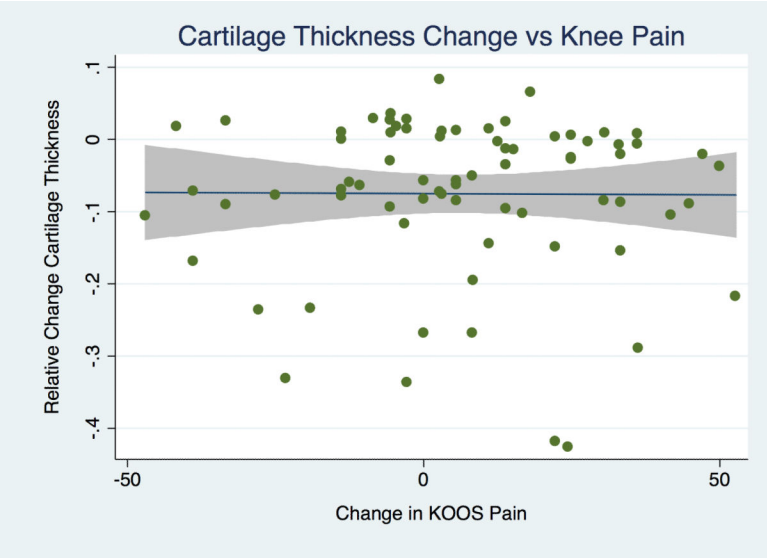

Fig. 4.

Linear regression (95% CI shaded gray) shows cartilage loss does not correlate with change in knee pain scores (r = −0.01).

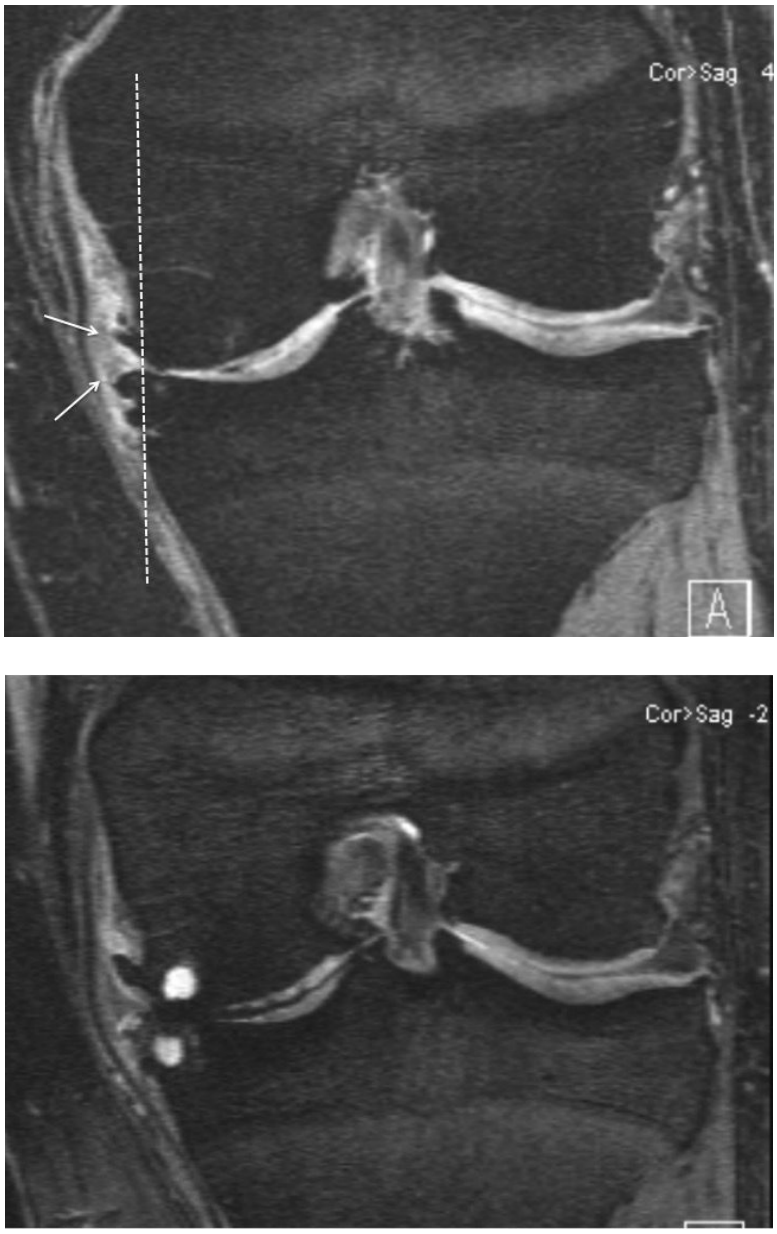

Fig. 5.

A 57-year-old man with severe meniscus extrusion and maceration. A) Coronal 3D DESS (dual-echo steady-state) sequence shows medial meniscus maceration (WORMS score 5) and extrusion (arrows) at initial MRI exam; dashed line represents expected medial boundary of meniscus at the medial plateau margin. B) Subsequent MRI at 48 months demonstrates progression of OA as evidenced by development of subchondral cysts; quantitative analysis revealed 34% cartilage loss in the medial compartment. His knee pain worsened over time, with KOOS pain score decreasing by 23 points.

Table 1

Meniscus Scoring Algorithm

Meniscus subsection scores were separately recorded for the medial meniscus anterior horn, body, and posterior horn. A single cumulative score was then generated according to WORMS scoring system [12]; for instance, if a non-displaced horizontal tear involving the body and posterior horn would be given a final score of 3.

Meniscus Subsection	Cumulative Score
0 Intact	**0** All subsection = 0
1 Minor radial / parrot-beak	**1** At least one 1, but no >1
2 Non-displaced / prior surgical repair	**2** 2 in only one region
3 Displaced / partially resected	**3** 2 in >1 region
4 Completely macerated	**4** 3 in ≥1 region
	5 4 in only 1 region
	6 4 in > 1 region

Table 2

Multiple regression with medial compartment cartilage thickness at 4 years as the outcome, and predictor variables including initial cartilage thickness, meniscus extrusion (present/absent), meniscus tear (present/absent), and demographic variables age, gender, and BMI (body mass index). The overall model was significant ($R^2 = 0.89$, $p < 0.0001$).

Predictor Variable	Coefficient	95% CI	p-value
Cartilage T_0	1.07	(0.96, 1.18)	**<0.001** *
Meniscus Extrusion	−0.33	(−0.47, −0.20)	**<0.001** *
Meniscus Tear	0.65	(−0.06, 0.19)	0.32
Age	−0.006	(−0.012, 0.001)	0.08
Male gender	−0.12	(−0.25, −0.01)	0.07
BMI	−0.002	(−0.013, 0.010)	0.75

* Initial cartilage thickness and meniscus extrusion were statistically significant predictors, with adjusted estimates of 1.07 mm increased 4-year cartilage thickness for every 1 mm thicker baseline cartilage measurement, and 0.33 mm cartilage decrease for presence of meniscus extrusion at baseline.