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Original article

Knee effusion volume assessed by magnetic resonance imaging and progression of knee osteoarthritis: data from the Osteoarthritis Initiative

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Abstract

Objective. To examine whether baseline knee joint effusion volume and the change in effusion volume over 1 year are associated with cartilage volume loss, progression of radiographic OA (ROA) over 4 years and risk of total knee replacement over 6 years.

Methods. This study included 4115 Osteoarthritis Initiative participants with knee joint effusion volume quantified by MRI at baseline. The change in effusion volume over 1 year was assessed. Cartilage volume loss and progression of ROA over 4 years were assessed using MRI and X-ray and total knee replacement over 6 years was assessed. Multiple linear regression and binary logistic regression were used for data analyses.

Results. Baseline knee effusion volume (per 5 ml) was positively associated with a loss of medial and lateral cartilage volume [regression coefficient 0.13%/year (95% CI 0.10, 0.17) and 0.13%/year (95% CI 0.10, 0.16), respectively, both $P < 0.001$], progression of ROA [odds ratio (OR) 1.28 (95% CI 1.20, 1.37), $P < 0.001$], and risk of knee replacement [OR 1.12 (95% CI 1.05, 1.20), $P = 0.001$]. A 5 ml increase in knee effusion volume over 1 year was positively associated with medial cartilage volume loss [regression coefficient 0.09%/year (95% CI 0.04, 0.15), $P = 0.001$], progression of ROA [OR 1.21 (95% CI 1.11, 1.33), $P < 0.001$] and risk of knee replacement [OR 1.24 (95% CI 1.12, 1.37), $P < 0.001$].

Conclusions. Knee joint effusion volume assessed from MRI provides a continuous and sensitive measure that was associated with cartilage volume loss, progression of ROA and risk of total knee replacement. It may provide a method to identify individuals with an inflammatory OA phenotype who are at higher risk of disease progression.

Key words: cartilage, knee OA, MRI, synovial effusion, total knee replacement

CLINICAL SCIENCE

Rheumatology key messages

- Knee joint effusion volume assessed from MRI was associated with structural progression of knee OA.
- Knee effusion volume may provide a method to identify individuals who have a higher risk of knee OA progression.

Introduction

There is increasing evidence that synovial inflammation plays an important role in the pathogenesis of knee OA [1–10]. Synovial inflammation can present as synovial membrane thickening and/or synovial fluid effusion. MRI is the imaging modality most commonly used to assess the presence and severity of synovial inflammation in OA research. Synovial membrane thickening and joint effusion as determined by MRI are often measured together as a whole with the term effusion-synovitis being used as a surrogate for synovial inflammation [2–10]. Using this methodology, previous studies have shown that effusion-synovitis predicts cartilage loss [2, 3], increased cartilage defects [5], development of knee OA [4, 9], knee pain [7] and knee replacement [6]. However, assessments of effusion-synovitis in these studies are based on the semi-quantitative measurement of capsular distension

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[11] and this method is limited by the possibility of misclassification. To date, there have been few studies applying a continuous measure of effusion-synovitis to sensitively examine its relationship with structural and clinical knee outcomes. A population-based cohort study reported that greater baseline effusion-synovitis maximal area was associated with increased knee cartilage defects, bone marrow lesions and cartilage volume loss over 2.7 years [8]. In people with knee OA, baseline effusion-synovitis volume was predictive of cartilage volume loss and increased effusion-synovitis volume was correlated with worsening knee pain and stiffness over 2 years [10].

Two studies have assessed synovial membrane thickening separately. A cross-sectional study found that synovial membrane volume measured with contrast-enhanced MRI was positively associated with the severity of radiographic knee OA, joint space narrowing and volume of subchondral bone marrow lesions [12]. Another study evaluating synovial membrane thickening using non-enhanced MRI showed a significant correlation between the severity of synovitis at baseline and the presence of medial meniscal extrusion and loss of cartilage volume at 60 days [13]. It has been shown that both synovial membrane volume and joint effusion volume, when measured separately from contrast-enhanced MRI, are correlated with histologic synovial inflammation, fibrin deposition, subsynovial mononuclear and polymorphonuclear leucocyte infiltration [14, 15].

Recently a means of quantifying knee joint effusion volume on non-contrast-enhanced MRI has been described and validated [16]. A fully automated system for MRI quantification of synovial effusion volume has demonstrated excellent correlations with manual quantification and direct aspiration of fluid [16]. As joint effusion volume is associated with synovial inflammatory activity [14], quantification of synovial effusion volume may be a sensitive predictor of the progression of knee OA and thus has the potential to identify individuals at risk for disease progression. This may facilitate targeting patients at risk of disease progression and optimize patient outcomes.

The current study aimed to determine whether baseline knee joint effusion volume and change in effusion volume over 1 year, quantified by MRI, predict cartilage volume loss, progression of radiographic OA (ROA) and risk of knee replacement in a large cohort of individuals with or at risk for knee OA.

Methods

OA *Initiative*

Data were extracted from the Osteoarthritis Initiative (OAI) database, a publicly available multicentre observational cohort study of knee OA (https://oai.epi-ucsf.org/datarelease/). The OAI comprises data of 4796 participants 45–79 years of age at baseline. OAI exclusion criteria included inflammatory arthritis, severe joint space narrowing in both knees, unilateral knee joint replacement and severe joint space narrowing in the contralateral knee, inability to undergo MRI or to provide a blood sample, required use of walking aids excepting a single straight cane $\leqslant$50% of the time or unwilling to provide informed consent. Participants were recruited at four clinical sites and the OAI study was approved by the institutional review boards at each of the sites. All participants gave informed consent; this study did not require additional approval. The follow-up retention rate was 78.8% at 4 years and 66.5% at 6 years.

Participants in the current study

Bilateral standing posteroanterior fixed-flexion knee radiographs [17] were obtained at baseline for Kellgren–Lawrence (KL) grading (0–4) ($n = 4369$). The data for these readings were obtained from the OAI database. If both knees had no evidence of ROA, the dominant knee was selected for analyses. If only one knee had evidence of ROA, this was the selected knee for analyses. If both knees had evidence of ROA, the knee with the highest KL grade was selected for analyses. When the severity was equal between sides, the most painful knee (i.e. with the highest WOMAC pain score) was selected for analyses. In the case of equal pain in both knees, the dominant knee was selected for analyses. The current study included participants with KL grade and knee joint effusion volume assessed at baseline ($n = 4115$).

Assessment of knee joint effusion volume

Knee MRI was performed for the target knee using a 3 T apparatus (Magnetom Trio, Siemens, Erlangen, Germany) and the exam consisted of a sagittal double-echo steady-state (DESS) sequence. Knee joint effusion volume was measured using a fully automated system in which the DESS sequence was used for bone and effusion segmentations, taking advantage of the DESS sequence T1 properties for the bone and T2 for the fluid, as previously described and validated [16]. The MRI quantification of effusion volume demonstrated excellent correlation coefficients with manual quantification ($r = 0.98$, $P < 0.0001$) and direct aspiration ($r = 0.88$, $P = 0.0008$) [16]. The change in effusion volume over 1 year was calculated as the 1-year follow-up volume − baseline volume; a positive value indicates an increase in effusion volume.

Assessment of knee cartilage volume

Knee cartilage volume was measured using automatic human knee cartilage segmentation, as previously described and validated [18]. Imaging was performed using a 3 T scanner and the exam consisted of a sagittal DESS sequence. Cartilage volume was analysed for the medial and lateral tibiofemoral compartments (i.e. condyle and plateau) [18], delineated as previously described [19] and implemented in the automated segmentation. The test–retest reliability revealed an excellent measurement error of 0.3 ± 1.6% for the global knee, corresponding to 30.3 ± 126.2 mm^3 [18]. The annual rate of cartilage volume loss over 4 years was obtained by (4-year follow-up volume − baseline volume)/baseline volume/4, in per cent.

Assessment of progression of ROA

Progression of ROA was defined by an increase in the KL grade of $\geqslant 1$ from baseline to the 4-year follow-up in participants with a baseline KL grade of 0–3.

Assessment of total knee replacement

At each available follow-up, participants indicated whether they had received total knee replacement surgery. Missing data for knee replacement were treated conservatively by assuming that the participant had not undergone knee replacement surgery. Knee replacement status was confirmed by the 6-year follow-up visit. It was defined as any knee with patient-reported total knee replacement that was confirmed on subsequent radiograph between baseline and the 6-year follow-up visit.

Data on intra-articular injections and knee injury

At baseline and the 1-year follow-up, participants were asked whether they had intra-articular injection of steroids in the past 6 months and whether they had ever injured their knees badly enough to limit their ability to walk for at least 2 days. From these data, the presence of intra-articular steroid injection in the past 6 months and injury in the past 12 months of the study knee was defined.

Statistical analyses

Demographic, clinical, radiological and MRI data were systematically entered into a computerized database. Descriptive statistics of participant characteristics were tabulated. The association between knee joint effusion volume and KL grade was examined using the Kruskal–Wallis test, as the data for effusion volume were not normally distributed. Multiple linear regression models were used to determine the relationship between baseline knee joint effusion volume (per 5 ml) and both medial and lateral cartilage volume loss over 4 years, adjusting for gender, baseline age, BMI, intra-articular steroid injection and knee injury. Multiple linear regression models were also used to determine the association between the change in effusion volume over 1 year (per 5 ml) and both medial and lateral cartilage volume loss over 4 years, adjusting for gender, baseline age, BMI, intra-articular steroid injection, knee injury and baseline effusion volume. Binary logistic regression models were used to determine the relationships of baseline knee joint effusion volume (per 5 ml) with the risk of progressive ROA over 4 years and knee replacement over 6 years, adjusting for gender, baseline age, BMI, KL grade, intra-articular steroid injection and knee injury. Binary logistic regression models were also used to determine the relationships of the change in effusion volume over 1 year (per 5 ml) with the risk of progressive ROA over 4 years and knee replacement over 6 years, adjusting for gender, baseline age, BMI, KL grade, intra-articular steroid injection, knee injury and baseline effusion volume. The interactions between effusion volume and KL grade for their association with the risk of progressive ROA and total knee replacement were examined by adding a term 'effusion volume*KL grade' to the logistic regression models and testing the significance. The associations were then examined separately for each KL grade. Multicollinearity was tested for each of the regression models using the variance inflation factor, where a value >10 would be a concern indicating multicollinearity. For regression analyses, both unadjusted and adjusted results were presented in the tables. All tests were two-sided and P-values <0.05 were considered statistically significant. Statistical analyses were performed using Stata 12.0 (StataCorp, College Station, TX, USA).

Results

Participant characteristics are shown in Table 1. Knee joint effusion volume was greater with increasing KL grade at baseline ($P < 0.001$). Over 1 year, the mean change in effusion volume was 0.1 ml (SD 5.5, range −58.8–62.3). Progression of ROA over 4 years was observed in 14.5% of the participants with a KL grade of 0–3 and 4.5% of the participants had a total knee replacement over 6 years, mostly (80.1%) in those with a KL grade of 3 or 4. The very low number of total knee replacements in participants with a baseline KL grade of 0 and 1 ($n = 7$) precluded meaningful analysis of total knee replacement risk in those individuals, so we performed analyses of total knee replacement only in those with a KL grade of 2–4 at baseline.

The relationships between baseline knee joint effusion volume (per 5 ml) and joint outcomes are shown in Table 2. After adjustment for gender, baseline age, BMI, intra-articular steroid injection and knee injury, baseline effusion volume was positively associated with the rates of medial [regression coefficient 0.13%/year (95% CI 0.10, 0.17), $P < 0.001$] and lateral (regression coefficient 0.13%/year (95% CI 0.10, 0.16), $P < 0.001$] cartilage volume loss. The variance inflation factor ranged from 1.00 to 1.04 for the independent variables included in these regression models. The P-values for the interaction between baseline effusion volume and KL grade were 0.052 for their association with progressive ROA and 0.005 for their association with total knee replacement. In participants with a baseline KL grade of 0–3, greater baseline effusion volume was associated with an increased risk of progressive ROA over 4 years [odds ratio (OR) 1.28 (95% CI 1.20, 1.37), $P < 0.001$]. The variance inflation factor ranged from 1.00 to 1.25 for the independent variables included in this regression model. The relationship remained significant in stratified analysis based on each individual KL grade, with the OR ranging from 1.20 to 1.61, and a significantly higher OR in the KL grade 1 group compared with the KL grade 3 group ($P = 0.02$). In participants with a baseline KL grade of 2–4, there was an increased risk of total knee replacement over 6 years with greater baseline effusion volume [OR 1.12 (95% CI 1.05, 1.20), $P = 0.001$]. The variance inflation factor ranged from 1.00 to 1.19 for the independent variables included in this regression model. In the stratified analysis of each individual KL grade, significant associations were seen in participants with KL grades 2 and 3, but not grade 4. The OR was significantly

Table 1 Characteristics of study participantss ($N = 4115$)

Characteristics	Values
Baseline	
Age, mean (S.D.), years	61.2 (9.1)
Female, *n* (%)	2383 (57.9)
BMI, mean (S.D.), kg/m^2	28.6 (4.8)
Knee joint effusion volume, median (IQR), ml	5.0 (3.2–8.5)
KL grade	
0 ($n = 1369$)	3.9 (2.8–5.5)
1 ($n = 663$)	4.3 (3.0–6.3)
2 ($n = 1102$)	5.4 (3.5–8.9)
3 ($n = 723$)	7.7 (4.8–14.9)
4 ($n = 258$)	15.8 (9.5–24.9)
Intra-articular steroid injection in the past 6 months, *n* (%)	50 (1.22)
Knee injury in the past 12 months, *n* (%)	42 (1.03)
Change	
Change in knee effusion volume over 1 year, ml ($n = 3867$), mean (S.D.; range)	0.1 (5.5; −58.8–62.3)
Annual % cartilage volume loss over 4 years ($n = 3138$)	
Medial compartment, mean (S.D.; range)	1.01 (1.62; −37.45–13.14)
Lateral compartment, mean (S.D.; range)	0.97 (1.26; −8.61–8.82)
Progression of radiographic OA over 4 years, *n* (%)	448 (14.5)
Baseline KL grade	
0 ($n = 1097$)	83 (7.6)
1 ($n = 555$)	108 (19.5)
2 ($n = 911$)	130 (14.3)
3 ($n = 534$)	127 (23.8)
Total knee replacement over 6 years, *n* (%)	186 (4.5)
Baseline KL grade	
0 ($n = 1369$)	3 (0.2)
1 ($n = 663$)	4 (0.6)
2 ($n = 1102$)	30 (2.7)
3 ($n = 723$)	74 (10.2)
4 ($n = 258$)	75 (29.1)

IQR: interquartile range.

Table 2 Associations between knee joint effusion volume (per 5 ml) at baseline and joint outcomes

	Unadjusted analysis Regression coefficient (95% CI)	*P*-value	Adjusted analysis Regression coefficient (95% CI)	*P*-value
Annual % medial cartilage volume loss[a]	0.16 (0.12, 0.20)	<0.001	0.13 (0.10, 0.17)	<0.001
Annual % lateral cartilage volume loss[a]	0.14 (0.11, 0.16)	<0.001	0.13 (0.10, 0.16)	<0.001
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Progression of radiographic OA over 4 years				
For KL grade 0–3[b]	1.34 (1.26, 1.42)	<0.001	1.28 (1.20, 1.37)	<0.001
For KL grade 0[a]	1.35 (1.07, 1.71)	0.01	1.44 (1.13, 1.84)	0.003
For KL grade 1[a]	1.43 (1.16, 1.77)	0.001	1.61 (1.26, 2.04)	<0.001
For KL grade 2[a]	1.31 (1.17, 1.47)	<0.001	1.33 (1.19, 1.50)	<0.001
For KL grade 3[a]	1.19 (1.09, 1.31)	<0.001	1.20 (1.09, 1.32)	<0.001
Total knee replacement over 6 years				
For KL grade 2–4[b]	1.26 (1.19, 1.33)	<0.001	1.12 (1.05, 1.20)	0.001
For KL grade 2[a]	1.35 (1.17, 1.55)	<0.001	1.35 (1.16, 1.56)	<0.001
For KL grade 3[a]	1.12 (1.00, 1.24)	0.04	1.14 (1.02, 1.27)	0.02
For KL grade 4[a]	1.04 (0.95, 1.14)	0.38	1.05 (0.95, 1.15)	0.32

[a]Multivariable models adjusted for gender, baseline age, BMI, intra-articular steroid injection and knee injury. [b]Multivariable models adjusted for gender, baseline age, BMI, KL grade, intra-articular steroid injection and knee injury.

Table 3 Associations between increasing knee joint effusion volume (per 5 ml) from baseline to 1 year and joint outcomes

	Unadjusted analysis Regression coefficient (95% CI)	*P*-value	Adjusted analysis Regression coefficient (95% CI)	*P*-value
Annual % medial cartilage volume loss[a]	0.02 (−0.04, 0.07)	0.51	0.09 (0.04, 0.15)	0.001
Annual % lateral cartilage volume loss[a]	−0.03 (−0.08, 0.01)	0.11	0.04 (−0.01, 0.08)	0.10
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Progression of radiographic OA over 4 years				
For KL grade 0–3[b]	1.13 (1.02, 1.25)	0.02	1.21 (1.11, 1.33)	<0.001
For KL grade 0[a]	1.45 (1.10, 1.91)	0.01	1.45 (1.12, 1.88)	0.004
For KL grade 1[a]	1.30 (1.03, 1.65)	0.03	1.38 (1.04, 1.83)	0.03
For KL grade 2[a]	1.04 (0.88, 1.23)	0.65	1.10 (0.94, 1.28)	0.23
For KL grade 3[a]	1.04 (0.89, 1.21)	0.62	1.20 (1.02, 1.41)	0.03
Total knee replacement over 6 years				
For KL grade 2–4[b]	1.15 (1.03, 1.28)	0.01	1.24 (1.12, 1.37)	<0.001
For KL grade 2[a]	1.00 (0.74, 1.37)	0.98	1.09 (0.87, 1.37)	0.46
For KL grade 3[a]	1.28 (1.08, 1.51)	0.005	1.32 (1.12, 1.56)	0.001
For KL grade 4[a]	1.16 (0.99, 1.37)	0.07	1.21 (1.02, 1.44)	0.03

[a]Multivariable models adjusted for gender, baseline age, BMI, effusion volume, intra-articular steroid injection, knee injury and intra-articular steroid injection and knee injury at 1 year. [b]Multivariable models adjusted for gender, baseline age, BMI, KL grade, effusion volume, intra-articular steroid injection, knee injury and intra-articular steroid injection and knee injury at 1 year.

higher in the KL grade 2 group compared with the KL grade 3 ($P = 0.04$) and grade 4 ($P = 0.002$) groups.

The relationships between the change (per 5 ml increase) in knee joint effusion volume over 1 year and joint outcomes are shown in Table 3. After adjustment for gender, baseline age, BMI, effusion volume, intra-articular steroid injection, knee injury and intra-articular steroid injection and knee injury at 1 year, increasing effusion volume over 1 year was positively associated with the rate of medial [regression coefficient 0.09%/year (95% CI 0.04, 0.15), $P = 0.001$] but not lateral [regression coefficient 0.04%/year (95% CI −0.01, 0.08), $P = 0.10$] cartilage volume loss. The variance inflation factor ranged from 1.01 to 1.18 for the independent variables included in these regression models. The *P*-values for the interaction between increasing effusion volume and KL grade were 0.21 for their association with progressive ROA and 0.23 for their association with total knee replacement. In participants with a baseline KL grade of 0–3, increasing effusion volume over 1 year was associated with an increased risk of progressive ROA over 4 years [OR 1.21 (95% CI 1.11, 1.33), $P < 0.001$]. The variance inflation factor ranged from 1.01 to 1.31 for the independent variables included in this regression model. The relationship remained significant in stratified analysis based on each individual KL grade, except for those with KL grade 2, with no significant difference in OR magnitude between groups. In participants with a baseline KL grade of 2–4, increasing effusion volume over 1 year was associated with an increased risk of total knee replacement over 6 years [OR 1.24 (95% CI 1.12, 1.37), $P < 0.001$]. The variance inflation factor ranged from 1.02 to 1.34 for the independent variables included in this regression model. In stratified analysis of each individual KL grade, significant associations were seen in participants with KL grades 3 and 4, but not grade 2, with no significant difference in OR magnitude between groups. Results were similar when progression of ROA was defined by an increase in KL grade $\geqslant 2$ from baseline to the 4-year follow-up (data not shown).

Discussion

This is the first study to demonstrate that both baseline knee joint effusion volume and an increase in effusion volume over 1 year, quantified from MRI, provide a continuous and sensitive measure that was associated with cartilage volume loss, progression of ROA and risk of total knee replacement in a large cohort of adults with or at risk for knee OA. MRI-quantified knee effusion volume may be used as a means to assist in identifying individuals at higher risk of knee OA progression.

This study, assessing knee joint effusion volume quantitatively from MRI using a fully automated system, supported and extended the findings from previous studies with synovial effusion and/or synovitis assessed from MRI semi-quantitatively [2–6, 9, 13] or quantitatively with manual segmentation [8, 10, 12]. The current study provides data, for the first time, demonstrating that knee joint effusion volume, as a continuous measure, is associated with the spectrum of joint degeneration in a large cohort of individuals with or at risk for knee OA. This spans from early stage cartilage volume loss, to the intermediary stage of progressive ROA, to end-stage disease requiring joint replacement surgery. These results were further contextualized when stratified analyses were performed based on baseline KL grade, where greater baseline effusion volume had adverse effects on disease progression

regardless of the radiographic grade of knee OA. We found consistent associations between greater baseline effusion volume and risk of progressive ROA in people with any KL grade from 0 to 3, but a stronger association in those with KL grade 1 compared with those with KL grade 3. This indicates a stronger association between knee effusion volume and the progression of ROA in individuals with mild knee OA when compared with those with moderate knee OA. The strongest association between baseline effusion volume and risk of total knee replacement was observed in those with KL grade 2 rather than those with KL grade 3 or 4, suggesting greater effusion volume would be a stronger risk factor for fast progression of OA requiring total knee replacement surgery within 6 years in those with mild ROA (KL grade 2). There was no significant association between baseline effusion volume and risk of total knee replacement in those with KL grade 4, indicating that greater effusion volume is no longer a risk factor for total knee replacement if people already have end-stage knee OA.

Our study examined whether the change in effusion volume from baseline to 1 year was associated with clinically important knee outcomes over 4–6 years. In our study population, the mean change in effusion volume over 1 year was 0.1 ml, but this varied widely, from a reduction of 58.8 ml to an increase of 62.3 ml. An increase in effusion volume, as a continuous measure, was associated with an increased risk of medial cartilage volume loss, progressive ROA and total knee replacement, independent of the radiographic grades of knee OA. Only one previous study investigated the change in effusion-synovitis volume over time as a continuous measure and found that increased effusion-synovitis volume was associated with worsening knee pain and stiffness over 2 years in people with knee OA [10]. Taken together, these findings suggest that the increase in effusion volume over time could be used to help identify individuals at risk of OA progression who should be targeted for intervention.

Knee OA is a heterogeneous condition with multiple phenotypes [20, 21]. The quantification of knee joint effusion volume using MRI may provide a method to identify those with an inflammatory OA phenotype who are at higher risk of disease progression. Randomized controlled trials of disease-modifying OA drugs are beginning to recruit participants based on the presence of specific phenotypes, including synovial effusion and/or synovitis [22, 23]. This could enable the selection of patients most likely to benefit from disease-modifying OA drugs, assisting the emergence of personalized or precision medicine to optimize patient outcomes. As the presence of synovial effusion and/or synovitis on MRI reflects synovial inflammation [14, 15], therapies with potent anti-inflammatory effects offer a theoretical construct for disease modification [22, 23]. However, most randomized controlled trials in this area have examined symptoms over short time periods rather than structures as the primary end point for potential disease-modifying OA drugs [24–26]. Data have suggested that chondroitin sulphate or combined chondroitin sulphate and glucosamine reduces joint swelling and effusion in knee OA [27, 28] and chondroitin sulphate reduces cartilage volume loss in knee OA patients with clinical signs of synovitis [29–31]. In contrast, a 2-year randomized, placebo-controlled trial of patients with symptomatic knee OA and ultrasonic features of synovitis showed that intra-articular triamcinolone, compared with intra-articular saline, resulted in significantly greater cartilage volume loss and no effect on knee pain and effusion volume [32]. More clinical trials are needed to determine the effects of therapies specifically targeting synovial inflammation on long-term joint outcomes in patients with specific phenotypes.

This study has limitations. Although our analyses were not adjusted for all the potential confounders, such as medications, as these data were limited, we were able to adjust for intra-articular injection of steroids in the past 6 months and knee injury in the past 12 months, which may influence effusion volume. Although the OAI offered a unique opportunity to study the disease profile of a large number of participants and explore the association between effusion volume and the spectrum of joint outcomes with long follow-up duration (4–6 years) and different structural measures, loss to follow-up may introduce bias. The retention rates were 78.8% at 4 years and 66.5% at 6 years. However, we found consistent results for cartilage volume loss and radiographic progression at 4 years and total knee replacement at 6 years.

The present study also has a number of strengths. The use of fully automated technologies to assess OA joint structural changes, including cartilage volume [18] and effusion volume [16], greatly improved the capacity and, more importantly, the reliability of the analysis. The change in effusion volume over time was investigated. This is important, as effusion volume may fluctuate with time, and thus an isolated baseline assessment may provide limited information about the effect of knee effusion volume on joint outcomes many years later.

This is the first study to demonstrate that knee joint effusion volume quantified from MRI provides a continuous and sensitive measure that is associated with long-term adverse joint outcomes, including cartilage volume loss, progression of ROA and risk of total knee replacement. It may provide a means to help identify individuals at higher risk of knee OA progression who should be targeted for intervention.

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References

1 Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol 2011;7:33–42.

2 Roemer FW, Guermazi A, Felson DT *et al*. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. Ann Rheum Dis 2011;70:1804–9.

3 Roemer FW, Zhang Y, Niu J *et al*. Tibiofemoral joint osteoarthritis: risk factors for MR-depicted fast cartilage loss over a 30-month period in the multicenter osteoarthritis study. Radiology 2009;252:772–80.

4 Roemer FW, Kwoh CK, Hannon MJ *et al*. What comes first? Multitissue involvement leading to radiographic osteoarthritis: magnetic resonance imaging-based trajectory analysis over four years in the osteoarthritis initiative. Arthritis Rheumatol 2015;67:2085–96.

5 Wang X, Blizzard L, Halliday A *et al*. Association between MRI-detected knee joint regional effusion-synovitis and structural changes in older adults: a cohort study. Ann Rheum Dis 2016;75:519–25.

6 Roemer FW, Kwoh CK, Hannon MJ *et al*. Can structural joint damage measured with MR imaging be used to predict knee replacement in the following year? Radiology 2015;274:810–20.

7 Wang X, Jin X, Han W *et al*. Cross-sectional and longitudinal associations between knee joint effusion synovitis and knee pain in older adults. J Rheumatol 2016;43:121–30.

8 Wang X, Blizzard L, Jin X *et al*. Quantitative assessment of knee effusion-synovitis in older adults: association with knee structural abnormalities. Arthritis Rheumatol 2016;68:837–44.

9 Atukorala I, Kwoh CK, Guermazi A *et al*. Synovitis in knee osteoarthritis: a precursor of disease? Ann Rheum Dis 2016;75:390–5.

10 Wang X, Jin X, Blizzard L *et al*. Associations between knee effusion-synovitis and joint structural changes in patients with knee osteoarthritis. J Rheumatol 2017;44:1644–51.

11 Peterfy CG, Guermazi A, Zaim S *et al*. Whole-organ magnetic resonance imaging score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage 2004;12:177–90.

12 Krasnokutsky S, Belitskaya-Levy I, Bencardino J *et al*. Quantitative magnetic resonance imaging evidence of synovial proliferation is associated with radiographic severity of knee osteoarthritis. Arthritis Rheum 2011;63:2983–91.

13 Pelletier JP, Raynauld JP, Abram F *et al*. A new non-invasive method to assess synovitis severity in relation to symptoms and cartilage volume loss in knee osteoarthritis patients using MRI. Osteoarthritis Cartilage 2008;16(Suppl 3):S8–13.

14 Ostergaard M, Stoltenberg M, Lovgreen-Nielsen P *et al*. Magnetic resonance imaging-determined synovial membrane and joint effusion volumes in rheumatoid arthritis and osteoarthritis: comparison with the macroscopic and microscopic appearance of the synovium. Arthritis Rheum 1997;40:1856–67.

15 Loeuille D, Sauliere N, Champigneulle J *et al*. Comparing non-enhanced and enhanced sequences in the assessment of effusion and synovitis in knee OA: associations with clinical, macroscopic and microscopic features. Osteoarthritis Cartilage 2011;19:1433–9.

16 Li W, Abram F, Pelletier JP *et al*. Fully automated system for the quantification of human osteoarthritic knee joint effusion volume using magnetic resonance imaging. Arthritis Res Ther 2010;12:R173.

17 Nevitt MC, Peterfy C, Guermazi A *et al*. Longitudinal performance evaluation and validation of fixed-flexion radiography of the knee for detection of joint space loss. Arthritis Rheum 2007;56:1512–20.

18 Dodin P, Pelletier JP, Martel-Pelletier J, Abram F. Automatic human knee cartilage segmentation from 3D magnetic resonance images. IEEE Trans Biomed Eng 2010;57:2699–711.

19 Raynauld JP, Kauffmann C, Beaudoin G *et al*. Reliability of a quantification imaging system using magnetic resonance images to measure cartilage thickness and volume in human normal and osteoarthritic knees. Osteoarthritis Cartilage 2003;11:351–60.

20 Dell'Isola A, Allan R, Smith SL, Marreiros SS, Steultjens M. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. BMC Musculoskelet Disord 2016;17:425.

21 Deveza LA, Melo L, Yamato TP *et al*. Knee osteoarthritis phenotypes and their relevance for outcomes: a systematic review. Osteoarthritis Cartilage 2017;25:1926–41.

22 Wang X, Hunter DJ, Jin X, Ding C. The importance of synovial inflammation in osteoarthritis: current evidence from imaging assessments and clinical trials. Osteoarthritis Cartilage 2018;26:165–74.

23 Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. Arthritis Res Ther 2017;19:18.

24 Arden NK, Reading IC, Jordan KM *et al*. A randomised controlled trial of tidal irrigation vs corticosteroid injection in knee osteoarthritis: the KIVIS Study. Osteoarthritis Cartilage 2008;16:733–9.

25 Abou-Raya A, Abou-Raya S, Khadrawi T, Helmii M. Effect of low-dose oral prednisolone on symptoms and systemic inflammation in older adults with moderate to severe knee osteoarthritis: a randomized placebo-controlled trial. J Rheumatol 2014;41:53–9.

26 Chevalier X, Goupille P, Beaulieu AD *et al*. Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 2009;61:344–52.

27 Hochberg MC, Martel-Pelletier J, Monfort J *et al*. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. Ann Rheum Dis 2016;75:37–44.

28 Clegg DO, Reda DJ, Harris CL *et al*. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006;354:795–808.

29 Martel-Pelletier J, Raynauld JP, Mineau F *et al*. Levels of serum biomarkers from a two-year multicentre trial are associated with treatment response on knee osteoarthritis cartilage loss as assessed by magnetic resonance imaging: an exploratory study. Arthritis Res Ther 2017;19:169.

30 Pelletier JP, Raynauld JP, Beaulieu AD *et al*. Chondroitin sulfate efficacy versus celecoxib on knee osteoarthritis structural changes using magnetic resonance imaging: a 2-year multicentre exploratory study. Arthritis Res Ther 2016;18:256.

31 Wildi LM, Raynauld JP, Martel-Pelletier J *et al*. Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. Ann Rheum Dis 2011;70:982–9.

32 McAlindon TE, LaValley MP, Harvey WF *et al*. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. JAMA 2017;317:1967–75.