Associations Between Knee Effusion-synovitis and Joint Structural Changes in Patients with Knee Osteoarthritis

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ABSTRACT. ***Objective.*** To describe the associations between effusion-synovitis and joint structural abnormalities in patients with knee osteoarthritis (OA) over 24 months.

Methods. A posthoc analysis using data from a randomized controlled trial in 413 patients with symptomatic OA (aged 63 ± 7 yrs, 208 women). Knee effusion-synovitis volume and score, cartilage defects, cartilage volume, and bone marrow lesions (BML) were assessed using magnetic resonance imaging. Joint space narrowing (JSN) and osteophytes were assessed using radiograph. Least significant change criterion was used to define change in effusion-synovitis volume. Knee symptoms were assessed by Western Ontario and McMaster University OA Index. Multivariable linear/logistic regression and multilevel generalized mixed-effects models were used in longitudinal analyses.

Results. Total effusion-synovitis volume increased modestly from baseline (8.0 ± 8.5 ml) to followup (9.0 ± 10.5 ml). Baseline BML, cartilage defect, JSN, and osteophyte scores were positively associated with change in effusion-synovitis volume ($p < 0.05$). Baseline cartilage defects and JSN were also associated with change in effusion-synovitis score ($p < 0.05$). However, neither baseline effusion-synovitis score nor volume consistently predicted change in the above structures except cartilage volume. In the mixed-effects models, knee effusion-synovitis was positively associated with BML (volume: $\beta = 1.19$ ml/grade; score: OR = 1.75/grade) and cartilage defects (volume: $\beta = 1.87$ ml/grade; score: OR = 2.22/grade), while negatively associated with cartilage volume loss. Change in effusion-synovitis volume was positively correlated with changes in knee pain and stiffness scores ($p < 0.05$).

Conclusion. Knee cartilage and subchondral bone abnormalities predicted change in effusion-synovitis, but effusion-synovitis did not predict knee structural changes. These findings suggest that synovial inflammation is likely the result of joint structural abnormalities in established OA. ClinicalTrials.gov identifier: NCT01176344. Australian New Zealand Clinical Trials Registry: ACTRN12610000495022. (J Rheumatol First Release September 1 2017; doi:10.3899/jrheum.161596)

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Osteoarthritis (OA) is the most common form of disabling arthritis among older people, leading to a tremendous individual and socioeconomic burden[1]. As a multifactorial disease, OA affects all joint structures including cartilage, subchondral bone, and synovium membrane[2,3,4]. Although the exact etiology of OA is still unclear, risk factors such as age, female sex, obesity, and injury have been identified as contributors to both onset and progression of OA[5]. Formerly considered a noninflammatory disease, it is now increasingly recognized that low-grade inflammation is involved in OA pathogenesis[6].

There is emerging evidence linking synovial inflammation and early OA[7,8,9]. Synovial activation (effusion and/or synovitis) has been suggested to be associated with OA

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outcomes such as radiographic alterations and total knee replacement[10,11]. It can also predict knee symptoms independent of other structural lesions[12,13]. Biologically, cartilage fragments could activate synovial abnormalities, and thus form a vicious, self-perpetuating cycle of local tissue lesions, inflammation, and repair[14].

Using non-contrast–enhanced magnetic resonance imaging (MRI), a combined assessment of synovial effusion and synovitis has been proposed, termed as "effusion-synovitis"[15]. We have validated an effusion-synovitis scoring system[16,17] based on the well-established whole-organ MRI score (WORMS) knee OA scoring system[18]. In an older population in which the majority had no or mild radiographic OA (ROA) but the vast majority had cartilage defects, we reported that baseline effusion-synovitis assessed in this way was independently associated with changes in knee cartilage defects and bone marrow lesions (BML)[16,19], but baseline knee cartilage defects and BML were not predictive of change in effusion-synovitis[19]. This suggests a possible causal relationship from effusion-synovitis to cartilage and bone structural changes, but not from structural changes to effusion-synovitis in early stages of knee OA. Because effusion-synovitis is observed throughout the entire course of OA[9], it is of interest to further investigate its involvement in more advanced stages of OA. To our knowledge, there is no clinical evidence regarding this in patients with established knee OA. Therefore, we aimed to investigate the associations between effusion-synovitis and joint structural abnormalities in patients with symptomatic knee OA over 24 months.

MATERIALS AND METHODS

Study design, setting, and participants. The Vitamin D Effect on Osteoarthritis (VIDEO) study was a randomized, double-blind, placebo-controlled clinical trial of patients with symptomatic knee OA and low vitamin D levels[20]. Our current analysis of data was from the VIDEO study, in which the study sample was analyzed as a cohort.

Participants were recruited in Tasmania and Victoria, Australia, using a combined strategy, including liaisons with general practitioners, specialist rheumatologists, and orthopedic surgeons, and advertising through media and community groups from August 2010 to December 2011. A telephone prescreen assessed knee pain, anticipated knee and hip surgery, participation in other studies, and comorbidities. Eligible participants were subsequently screened in a clinic visit including knee radiographs and a blood test for serum 25-hydroxy vitamin D (25(OH)D) level.

Eligible participants were aged between 50 to 79 years with symptomatic knee OA for at least 6 months and pain of at least 20 mm on a 100-mm visual analog scale. All individuals were assessed according to the American College of Rheumatology criteria for symptomatic knee OA[21]. Participants were excluded if they had grade 3 knee ROA according to the Osteoarthritis Research Society International (OARSI) atlas[22], contraindication to MRI, and other rheumatic diseases. Detailed inclusion and exclusion criteria have been given in the initial report[20]. Ethics approval was received from the Tasmania Health and Human Medical Research Ethics Committee (reference number H1040) and Monash University Human Research Ethics Committee (reference number CF10/1182-2010000616). Informed written consent was obtained from all participants.

MRI and image processing. High-resolution non-contrast–enhanced knee MRI acquisitions were obtained at baseline and 24 months on a 1.5T whole-body MRI unit (Picker) using a commercial transmit-receive extremity coil. Image sequences included the following: (1) T1-weighted sagittal fat-suppressed 3-D gradient-recalled acquisition in the steady state, flip angle 30°, repetition time 31 ms, echo time 6.71 ms, field of view (FOV) 16 cm, 60 partitions, 512 × 512–pixel matrix, acquisition time 5 min 58 s, 1 acquisition; slice thickness of 1.5 mm without a between-slice gap; and (2) T2-weighted sagittal fat-suppressed fast spin echo (FSE), flip angle 90°, repetition time 3067 ms, echo time 112 ms, FOV 16 cm, 45 slices, 228 × 256-pixel matrix, slice thickness of 2 mm; or proton density-weighted coronal fat-suppressed FSE, flip angle 90°, repetition time 3400 ms, echo time 64 ms, FOV 16 cm, 30 slices, 256 × 256-pixel matrix, acquisition time 5 min 26 sec, 1 acquisition, slice thickness of 3 mm.

Effusion-synovitis volume. The total volume of the joint was isolated by selecting regions of interest according to the intraarticular fluid-equivalent signal on a section-by-section basis (Figure 1A). The final 3-D volume rendering was generated using commercial in-house OsiriX Lite imaging software cursors (32-bit version 5.9, Pixmeo SARL; Figure 1B)[23]. A musculoskeletal researcher with 3 years of experience (XW) and an orthopedic clinician with 7 years of experience (WH) measured the volume of effusion-synovitis under the guidance of an experienced radiologist with > 20 years of experience. The serial MRI were measured in pairs by 2 independent readers who were blinded to the treatment allocation and patients' information. The 2 readers assessed 40 randomly selected images with at least a 4-week interval between readings. The intrarater reliability [expressed as intraclass correlation coefficient (ICC)] was 0.96–0.97 and interrater reliability was 0.93–0.99 in different subregions.

Change in effusion-synovitis volume was calculated as from baseline to Month 24. A least significant change (LSC) criterion was used to define an increase and no increase (stable or a decrease) in effusion-synovitis volume. This takes into account measurement error and the correlation between the baseline and followup measurements[24]. The formula was as follows (σ = the standard error of the mean; ρ = the serial correlation):

$$LSC = 1.96 \times \sigma \sqrt{[2\ (1 - \rho)]}$$

For example, LSC of total effusion-synovitis volume was calculated to be 1.81 ml (where $\sigma = 1.17$ and $\rho = 0.69$) in our study. Therefore, participants were categorized as having an increase in effusion-synovitis volume if the change in effusion-synovitis volume was ≥ +1.81 ml, and having no increase effusion-synovitis if the change was < +1.81 ml[25].

Effusion-synovitis score. Effusion-synovitis was scored according to a modified WORMS method, grading collectively from 0 to 3 based on the estimated maximal distension of the synovial cavity: grade 0 = normal, grade 1 = ≤ 33% of maximum potential distension, grade 2 = 33–66% of maximum potential distension, and grade 3 = ≥ 66% of maximum potential distension[18]. The interrater reliability was 0.63–0.75 and intrareader reliability was 0.60–0.75 (weighted κ) in different subregions as described previously[16].

Change in effusion-synovitis score was calculated as the score at Month 24 minus score at baseline.

Cartilage volume. Baseline and followup knee cartilage volume (medial tibial, lateral tibial, and patellar) was assessed on T1-weighted MRI, determined by image processing on an independent workstation using OsiriX software[26]. The volumes of individual cartilage plates were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 μm × 312 μm with 1.5-mm thickness, continuous sections) for the final 3-D rendering. The rate of change in cartilage volume was calculated as follows:

$$\text{percentage change per annum} = [(\text{absolute change} \div \text{baseline cartilage volume}) \div (\text{time between 2 scans, in yrs})] \times 100$$

The coefficients of variation (CV) for this method were 2.1–2.6% as described in our previous study[27].

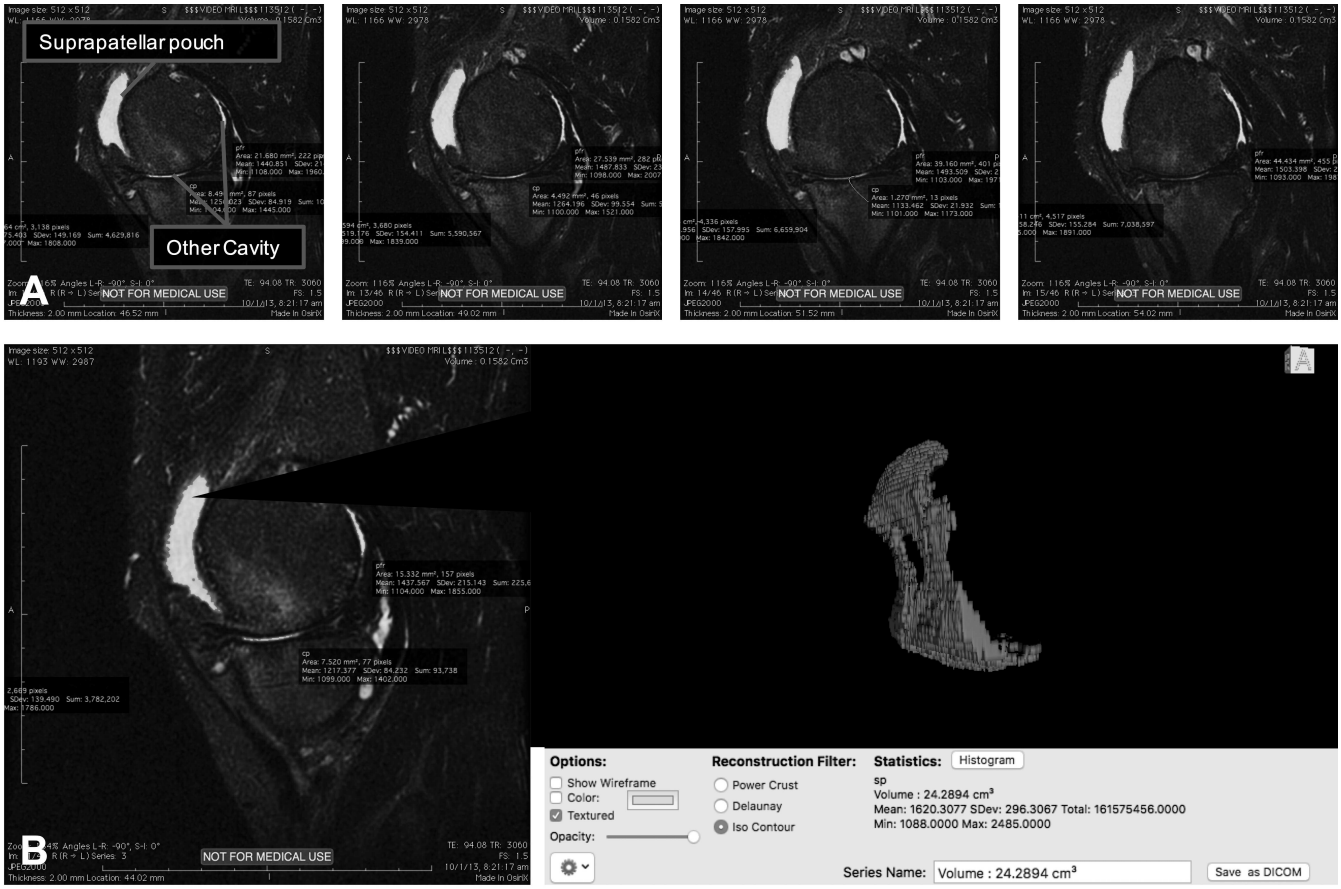

Figure 1. Magnetic resonance images acquired from the knee, with superimposed color data showing the area of fluid-equivalent hyposignals. (A) Representative sagittal image examples were selected from the consecutive slices. The total volume was generated from the highlighted areas (suprapatellar pouch and other cavity) in the entire series of images using OsiriX software. (B) An example of 3-D reconstruction of segmented suprapatellar pouch effusion-synovitis.

Cartilage defect. Cartilage defects were graded using a modified Outerbridge classification[28] at medial tibial, medial femoral, lateral tibial, and lateral femoral sites: grade 0 = normal cartilage, grade 1 = focal blistering and intracartilaginous hyperintensity with a normal contour, grade 2 = irregularities on the surface and loss of thickness of < 50%, grade 3 = deep ulceration with loss of thickness of > 50% without exposure of subchondral bone, and grade 4 = full thickness chondral wear with exposure of subchondral bone. A highest score of all sites was chosen as the total score of the whole joint, ranging from 0 to 4. A change in the cartilage defect score was calculated by subtracting baseline score from followup score. Intraobserver reliability was 0.77–0.94 (expressed as ICC) at different sites. Interobserver reliability was assessed in 50 MR images and yielded ICC of 0.85–0.93 at different sites[26].

Bone marrow lesion. Subchondral BML were defined as discrete areas of increased signal adjacent to the subcortical bone. The areas were measured semiquantitatively using the modified WORMS method[18]. BML were scored from 0 to 3 based on the extent of subregional involvement: grade 0 = none, grade 1 = ≤ 25% of the subregion, grade 2 = 25–50%, and grade 3 = > 50%. A highest score of all sites was chosen as the total score of the whole joint, ranging from 0 to 3. A change in BML was calculated. The intraobserver repeatability was assessed in 50 participants with ICC from 0.89–1.00 at different sites[29].

Knee radiographic measurements. Knee radiographic abnormalities were assessed at baseline only by a standing semiflexed anterior-posterior radiograph using the OARSI atlas as previously described[22,30]. Each of the following was assessed from 0–3: medial JSN, lateral JSN, medial femoral osteophytes, medial tibial osteophytes, lateral femoral osteophytes, and lateral tibial osteophytes. A highest score of all sites was chosen as the total score of the whole joint, ranging from 0 to 3. Scores for each participant were determined by consensus of 2 readers. Intraobserver repeatability was assessed in 40 participants with ICC from 0.65 to 0.85 as previously reported[31].

Knee symptoms. Knee symptoms were assessed from baseline to Month 24 using the Western Ontario and McMaster Universities OA Index (WOMAC) score[32]. The WOMAC system quantifies the degree of pain (5 questions), functional impairment (17 questions), and stiffness (2 questions) in patients with OA. Each question was assessed in a 100-mm visual analog format and a total score was created.

Additional data. Height and weight were measured at the baseline and followup clinic visits. Body mass index (BMI) was calculated using weight (in kg) divided by square of height (in m^2).

Serum (25(OH)D) was assayed at baseline and followup by Liaison method using a direct competitive chemiluminescent immunoassays (DiaSorin Inc). The intraassay and interassay CV were 3.2% and 6.0%.

Statistical analysis. Baseline characteristics were compared between 2 groups with the use of Student t tests or chi-square tests. Multivariable logistic regressions (binary and ordinal as appropriate) were performed using generalized linear models to test the associations between independent variables and dependent variables after adjustments for age, sex, BMI, study site, and intervention. The proportional odds assumption was tested for the ordered logistic regressions.

Associations between effusion-synovitis and structural outcomes over study period were estimated using multilevel generalized mixed-effects linear or ordinal logistic regression models, which allow for more appropriate adjustments for repeated measures and protection against bias for missing data[33]. Mixed-effects models imply that there are "fixed" effects as well as "random" effects. In longitudinal analyses, we used random intercepts for individual participants and fixed effects of age, sex, BMI, study site, and intervention. Both unadjusted and adjusted associations between effusion-synovitis and structural measures were expressed as maximum-likelihood estimated slope coefficients.

All the data analysis was performed on Stata V13.0 (Stata Corp). A 2-sided p value of 0.05 indicated statistical significance.

RESULTS

Participants. In total, 413 patients (257 from Hobart and 152 from Melbourne) aged between 49 and 80 years (mean 63 ± 7 yrs) with equal sex proportion participated in our study. Four patients were excluded because their MRI measures were unavailable at baseline. Over 24 months, 340 patients (83%) completed the followup as described elsewhere[20]. There were no significant demographic differences between those who completed and those who were lost to followup (data not shown).

Table 1 shows the comparisons of baseline characteristics between participants who had an increase and no increase (stable and decrease) in effusion-synovitis volume (defined by the LSC). The prevalence of an increase and no increase in effusion-synovitis was 32% and 68%, respectively. An increase in effusion-synovitis volume was lower in women and participants randomized to vitamin D supplementation. Participants with increased effusion-synovitis volume had higher prevalence of BML, but lower knee pain score. There were no other significant differences between groups in age, BMI, knee injury, and cartilage morphology.

Quantitative and semiquantitative measures of effusion-synovitis. At baseline, the mean size of effusion-synovitis was 8.0 ± 8.5 ml, ranging from 0.2 ml to 59.1 ml. Over 24 months of followup, the mean size of effusion-synovitis changed to 9.0 ml (SD 10.5 ml).

The prevalence of effusion-synovitis at baseline was 48% (score ≥ 2). At 24 months, the prevalence of effusion-synovitis was 51%. Twenty-three percent of participants had an increase (change in score ≥ 1) and 17% had a reduction (change in score ≤ –1) in grade of effusion-synovitis over 24 months.

Associations between effusion-synovitis and knee structures. Baseline tibiofemoral BML, cartilage defects, osteophytes, and JSN were all positively associated with the increase in effusion-synovitis volume, after adjustments for age, sex, BMI, study site, and intervention (Table 2). No significant associations were found between baseline cartilage volume and increases in effusion-synovitis volume (Table 2). When the change in effusion-synovitis score was used as the outcome, only baseline total cartilage defects and total and tibiofemoral JSN were significantly associated with this outcome (Table 2).

Conversely, baseline effusion-synovitis volume was not associated with changes in other structures including cartilage defects, cartilage volume, and BML. Baseline effusion-synovitis score was negatively associated with the change in tibial cartilage volume, but not with changes in cartilage defects and BML in multivariable analyses (Table 3).

Using mixed-effects models, effusion-synovitis volume

Table 1. Participant characteristics at baseline. Student t test or chi-square test was used for the comparison. Values are % (n) unless otherwise specified.

Characteristics	Effusion-synovitis Volume Change Defined by Least Significant Change Criterion		p
	No Increase, n = 239	Increase, n = 115	
Age, yrs, mean (SD)	63.2 (7.1)	63.1 (7.2)	0.96
Women	55 (131)	41 (48)	**0.01**
BMI, kg/m^2, mean (SD)	29.4 (4.8)	30.1 (5.2)	0.24
Plasma 25-hydroxyvitamin D, nmol/l, mean (SD)	43.7 (11.8)	44.6 (13.1)	0.55
Vitamin D supplementation	56 (134)	41 (47)	**0.01**
Past knee injury	8 (19)	6 (7)	0.67
Past knee surgery	18 (43)	23 (26)	0.31
Bone marrow lesion	75 (179)	88 (101)	**< 0.01**
Cartilage defect	97 (232)	99 (114)	0.22
Cartilage volume, ml, mean (SD)	5.7 (1.7)	5.9 (1.6)	0.35
Osteophyte	84 (201)	90 (103)	0.14
Joint space narrowing	90 (215)	93 (107)	0.38
WOMAC questionnaire			
Knee pain, range 0–500, mean (SD)	143.0 (87.4)	119.8 (76.9)	**0.02**
Knee function, range 0–1700, mean (SD)	489.2 (314.2)	440.6 (278.5)	0.16
Knee stiffness, range 0–200, mean (SD)	64.5 (41.2)	58.1 (37.5)	0.17

Statistically significant difference at $\alpha = 0.05$ are in bold face. BMI: body mass index; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2. Associations between baseline knee structural abnormalities and change in effusion-synovitis over 24 months. Dependent variable: an increase in effusion-synovitis over 24 months. Independent variable: baseline knee structures.

Knee Structures	Volume Change#, RR (95% CI)	Score Change*, OR (95% CI)
Bone marrow lesion, 0–3		
Total	**1.31 (1.14–1.49)**	1.03 (0.84–1.25)
Tibiofemoral	**1.30 (1.15–1.48)**	1.01 (0.83–1.22)
Patellar	1.04 (0.88–1.22)	1.01 (0.79–1.29)
Cartilage defect, 0–4		
Total	**1.66 (1.15–2.40)**	**1.43 (1.05–1.95)**
Tibiofemoral	**1.38 (1.13–1.69)**	1.16 (0.91–1.46)
Patellar	1.01 (0.88–1.15)	1.18 (0.98–1.43)
Cartilage volume, ml		
Total	0.90 (0.79–1.03)	0.84 (0.70–1.00)
Tibial	0.87 (0.72–1.05)	0.83 (0.64–1.08)
Patellar	0.92 (0.75, 1.14)	0.80 (0.59–1.07)
Osteophyte, 0–3		
Total	**1.40 (1.18–1.66)**	1.04 (0.82–1.32)
Tibiofemoral	**1.44 (1.23–1.70)**	1.06 (0.83–1.36)
Patellar	**1.31 (1.12–1.53)**	1.05 (0.82–1.34)
Joint space narrowing, 0–3		
Total	**1.55 (1.26–1.91)**	**1.40 (1.05–1.85)**
Tibiofemoral	**1.80 (1.42–2.28)**	**1.56 (1.11–2.20)**
Patellofemoral	**1.18 (1.00–1.38)**	1.21 (0.95–1.53)

Generalized binary# and ordinal* logistic regression models were used, after adjustment for age, sex, body mass index, site, and intervention. #Effusion-synovitis volume change was dichotomized using least significant change criterion. Statistically significant differences at $\alpha = 0.05$ are in bold face.

Table 3. Associations between baseline effusion-synovitis and change in knee structural abnormalities. Dependent variable: change in knee structures over 24 months. Independent variable: baseline effusion-synovitis.

Knee Structures	Volume, ml#, β (95% CI)	Score, 0–3*, OR (95% CI)
Bone marrow lesion, 0–3		
Total	0.32 (–0.71 to 1.34)	1.05 (0.84–1.32)
Tibiofemoral	–0.20 (–1.23 to 0.82)	1.05 (0.78–1.40)
Patellar	0.07 (–0.99 to 1.13)	0.89 (0.71–1.11)
Cartilage defect, 0–4		
Total	–1.35 (–3.09 to 0.39)	0.74 (0.46–1.20)
Tibiofemoral	0.03 (–1.29 to 1.34)	1.10 (0.78–1.56)
Patellar	–0.54 (–2.03 to 0.96)	1.08 (0.77–1.52)
Cartilage volume, ml		
Total	–0.07 (–0.25 to 0.10)	0.97 (0.93–1.01)
Tibial	–0.17 (–0.35 to 0.01)	**0.94 (0.90–0.98)**
Patellar	0.04 (–0.06 to 0.13)	1.01 (0.98–1.03)

Generalized linear# and ordinal* regression models were used, after adjustment for age, sex, body mass index, site, and intervention. Statistically significant differences at $\alpha = 0.05$ are in bold face.

was positively associated with total and tibiofemoral cartilage defects and BML over 24 months, and negatively associated with the change in total and tibial cartilage volume after adjustments (Table 4). The associations between effusion-synovitis score and above structural changes were largely consistent with the results for effusion-synovitis volume (Table 4).

Associations between effusion-synovitis and knee symptoms. Table 5 shows the longitudinal associations between change in effusion-synovitis volume and change in WOMAC score over 24 months after adjustment. Change in effusion-synovitis volume was positively associated with changes in WOMAC pain and stiffness scores. There were no significant associations between baseline effusion-synovitis score and changes in knee symptoms (data not shown).

DISCUSSION

Our study described the dynamic changes in effusion-synovitis over 24 months in patients with symptomatic knee OA. We found that baseline JSN, osteophytes, cartilage defects, and BML were associated with change in effusion-synovitis, but baseline effusion-synovitis was not signifi-

Table 4. Longitudinal associations between effusion-synovitis and other structural abnormalities over 24 months. Dependent variable: effusion-synovitis at baseline and Month 24. Independent variable: knee structures at baseline and Month 24. Generalized mixed-effects linear regression models were used in all analyses, after adjustment for age, sex, body mass index, site, and intervention.

Knee Structures	Volume, ml, β (95% CI)	Score, 0–3, OR (95% CI)*
Bone marrow lesion, 0–3		
Total	**1.19 (0.39–1.98)**	**1.75 (1.34–2.28)**
Tibiofemoral site	**1.50 (0.65–2.36)**	**2.05 (1.57–2.67)**
Patellar site	–0.47 (–1.23 to 0.28)	1.03 (0.73–1.44)
Cartilage defect, 0–4		
Total	**1.87 (1.06–2.69)**	**2.22 (1.46–3.38)**
Tibiofemoral site	**1.74 (0.89–2.59)**	3.01 (1.51–6.02)
Patellar site	–0.15 (–0.80 to 0.50)	1.04 (0.79–1.36)
Cartilage volume, ml		
Total	**–0.83 (–1.42 to –0.24)**	0.80 (0.64–1.02)
Tibial site	**–2.19 (–3.22 to –1.16)**	**0.63 (0.44–0.89)**
Patellar site	0.52 (–0.61 to 1.64)	0.99 (0.66–1.49)

*Generalized mixed-effects ordinal logistic regression models were used for ordinal outcomes. Statistically significant differences at $\alpha = 0.05$ are in bold face.

Table 5. Associations between change in WOMAC scores and change in effusion-synovitis volume. Generalized linear regression models were used, after adjustment for age, sex, body mass index, site, and intervention. Values are β (95% CI).

WOMAC Scores	Effusion-synovitis Volume
Pain	**2.34 (0.62–4.06)**
Function	4.69 (–0.34 to 9.73)
Stiffness	**0.92 (0.14–1.71)**

Statistically significant difference at $\alpha = 0.05$ are in bold face. WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

cantly associated with cartilage and bone structural changes except tibial cartilage volume. Further, changes in knee OA outcomes, including cartilage defects, cartilage volume, BML, and knee symptoms were all significantly associated with change in effusion-synovitis over 24 months. These suggest that cartilage and bone structural abnormalities may be the cause of effusion-synovitis in patients with established knee OA. Effusion-synovitis might not play a major role in the progression of structural changes in knee OA while possibly coexisting with this pathology.

The exact pathophysiological mechanisms that lead to synovial inflammation in OA are not well understood. There is a possible link between activated synovial inflammation and the degradation of adjacent structures. Cartilage matrix fragments, which are released into the joint fluids, could be detected as foreign bodies or neo-antigens by the synovium. They may trigger a secondary immune response and inflammatory reaction in OA[34,35]. There is no longitudinal evidence suggesting that subchondral bone lesions can lead to synovial inflammation in knee OA. In this OA population, we found that baseline structural changes including JSN, osteophytes, cartilage defects, and BML were all positively associated with changes in effusion-synovitis, suggesting that cartilage breakdown and erosive subchondral bone could induce and exacerbate synovial inflammation in established albeit mild knee OA.

In our previous study, we examined synovial abnormalities in an elderly population largely with asymptomatic or early OA, and found that baseline effusion-synovitis was associated with cartilage defects and BML over 2.6 years[16]. In our current study, we found that baseline effusion-synovitis was not associated with structural deterioration. The major difference between the populations of our 2 studies is that there was more severe chondropathy and more subchondral bone erosions in the VIDEO study where participants had symptomatic knee OA (cartilage defects 98%; cartilage volume 5.7 ± 1.7 ml; BML 79%) than in the previous older adult cohort (cartilage defects 53%; cartilage volume 8.3 ± 2.0 ml; BML 36%). However, the longitudinal changes in those structures were largely comparable in both cohorts. For example, an increase in BML is 32% versus 24% in older adults[36] and an increase in cartilage defects is 49% in the current study compared to 33%[37]. Thus, the high baseline prevalence of these abnormalities will not result in negative findings in the VIDEO cohort. To get unbiased results from the longitudinal data, we applied mixed-effects models where subject-specific random effects were used to tie together the observations from the same subject. The mixed-effects model automatically computes correct standard errors for random and fixed effects. It not only allows unbalance or missing observations within subjects, but also unequal time intervals and various within-subject covariance factors, such as demographic characteristics[33]. Considering our previous findings that effusion-synovitis was indirectly associated with worsening in BML and cartilage abnormalities in early OA[16], our current findings suggested that there might be complex mutual effects involved in these structural abnormalities during different stages of disease progression.

Interestingly, the associations between effusion-synovitis and structural abnormalities were consistent in the tibiofemoral compartment, but not in the patellar compartment. This was consistent with a study that reported that synovitis or effusion was associated with an increased risk for focal cartilage loss in the tibiofemoral compartment, but not in the patellofemoral compartment[7]. The underlying mechanisms are unclear, but mechanical and constitutional factors may contribute to this site-specific variation[38]. With regard to the anatomic distribution, the suprapatellar pouch of the knee joint is the most common site for detecting abnormal synovial alterations[39]. Although we did not find that suprapatellar effusion-synovitis had site-specific associations with patellar cartilage or patellar subchondral bone lesions, it is possible that the dynamic inflammation response in established OA is more likely to be diffuse rather than localized.

We found that cartilage defects, but not quantitative cartilage volume, was significantly associated with change in joint effusion-synovitis. In fact, cartilage defects are evaluated on the cartilage surface morphology by the extent and depth of cartilage lesions, and debris released from cartilage lesions to joint cavity may induce effusion-synovitis. In contrast, cartilage volume measures the status of cartilage loss in the whole plate rather than focal sites so it may not identify cartilage debris releasing from local sites.

Accurate quantification of synovial inflammation will improve understanding of its natural history. Some widely used semiquantitative assessments of effusion-synovitis, such as WORMS and the Knee Osteoarthritis Scoring System, are subjective and require scoring from experienced professionals[18,40]. There is still conflicting evidence regarding the association of structural alterations with the severity of synovitis, which is possibly because of inconsistent scoring systems and imaging tools[41,42,43,44]. Our study applied a semiautomatic segmentation method that accurately generated the 3-D volume reconstruction from the area of effusion-synovitis in MR images. It was highly reproducible (ICC 0.93–0.99) and could be picked up easily by inexperienced readers. Further, we tested the volume measurement with the previous semiquantitative assessment, which showed a high correlation (r = 0.71). Importantly, more significant associations of baseline knee structures were found with change in effusion-synovitis volume than score, suggesting this validated measuring system may be more sensitive than semiquantitative measures.

There are some potential limitations in our study. As a posthoc analysis, the original randomized controlled trial was not designed to study the associations between synovial

inflammation and knee structural changes, and our results are only generalizable to patients with established knee OA and low vitamin D levels. However, the sample size in the original trial had sufficient power (> 90%) to address the research question in our current study. Last, we used non-contrast–enhanced MRI, which was unable to differentiate synovial fluid and synovial thickening, so measurement of effusion-synovitis may not actually reflect synovitis status.

Knee cartilage and subchondral bone abnormalities predicted change in effusion-synovitis, but effusion-synovitis mainly did not predict knee structural changes. These findings suggest that synovial inflammation is most likely the result of joint structural abnormalities in established OA.

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