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Associations between clinical evidence of inflammation and synovitis in symptomatic knee osteoarthritis: a substudy of the VIDEO trial

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Abstract

Objective

Painful knee osteoarthritis (KOA) has been associated with joint inflammation. There is however little literature correlating signs of localised inflammation with Contrast-enhanced (CE) Magnetic resonance imaging (MRI) of synovium. This study examined the relationship between clinical and functional markers of localised knee inflammation and CE MRI based synovial scores.

Methods

Patients with symptomatic KOA were enrolled into the randomised, double-blind, Vitamin D Evaluation in Osteoarthritis (VIDEO) trial. In this cross-sectional substudy, associations between validated MRI based semi-quantitative synovial scores of the knee and the following markers of inflammation were investigated; self-reported pain and stiffness, effusion, warmth, joint line tenderness, erythrocyte sedimentation rate, radiographic severity and functional ability tests.

Results

107 patients satisfied the inclusion criteria of complete data and were included in the analysis. Significant associations were found between the number of regions affected by synovitis and WOMAC pain, effusion and joint line tenderness. Each additional region affected by synovitis was associated with an increase in WOMAC pain (1.82; 95% CI 0.05-3.58; p=0.04) and the association with extent of medial synovitis was particularly strong (3.21; 95% CI 0.43-5.99; p=0.02). Extent of synovitis was positively associated with effusion (OR=1.69; 95% CI 1.37-2.08, p<0.01), and negatively associated with joint line tenderness (RR= 0.87; 95% CI 0.84-0.90; p<0.01).

Conclusion

There is a strong positive association between synovitis, and self-reported patient pain and clinically detectable effusion. Non-operative treatments directed at management of inflammation and future trials targeting the synovial tissue for treating KOA should consider these two factors as potential inclusion criteria.

Keywords: Synovitis, Knee Osteoarthritis, Inflammation.

Significance & Innovation

- Knee synovitis is associated with clinically detectable effusion and knee pain.
- Joint line tenderness is negatively associated with synovial inflammation.
- We found no correlation between warmth or stiffness and the extent of synovitis.
- These findings suggest that treatments targeting synovitis might be most effective in individuals with knee osteoarthritis associated with clinically detectable effusion.

1. Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis and a major cause of morbidity worldwide. Synovitis, inflammation of the synovial lining, may be present from the onset of OA, tends to increase with radiographic severity and may contribute to the worsening of chondral lesions (1). Synovial samples in OA are histologically similar to those of rheumatoid arthritis (RA), but are characterized by a trend toward lower cell density (2-4).

The majority of people with knee pain will have no radiographic changes associated with knee osteoarthritis (KOA) and less than 50% of individuals with radiographic KOA will report knee pain(5). Microscopic synovitis scores are however greater in individuals with symptomatic chondral changes compared with asymptomatic individuals (6). Knee pain with or without radiological evidence of osteoarthritis is associated with significantly increased risk of early cardiovascular mortality in middle-age women (7). Even after adjusting for baseline cartilage damage and meniscal tears and extrusions, high levels of synovitis are independently associated with new incident of radiographic KOA(8).

Contrast-enhanced (CE) Magnetic Resonance Imaging (MRI) permits differentiation of inflamed and non-inflammed synovium and is a valuable tool in evaluating synovitis in OA (2, 9-13). Only Gd-DTPA–enhanced T1-weighted sequences have the documented ability to enable accurate quantification of inflamed synovium (location-specific synovial thickening, volume and rate of synovial enhancement on dynamic sequences) resulting in a good association with macroscopic and microscopic scores in OA, RA and in spondylarthropathy (9, 14-20). Synovial thickening has

been demonstrated on T2-weighted MRI sequences in 73% of joints with early OA (21) and the strong association of knee synovitis with radiographic OA severity and cartlige damage has been reported (22).

Inflammation is classically associated with the five clinical signs: tumor(swelling), dolor(pain), rubor(redness), calor (heat), and functio laesa(disturbance of function). A cohort study of OA subjects demonstrated that moderate and large effusions with capsular distension and synovial thickening were significantly more common among those with knee pain, however, no functional evaluation was made [19]. In KOA pain is strongly associated with synovitis, this association is stronger than with other intra-articular lesions.(23)

The aim of this study was to investigate whether self-reported knee pain and other clinical, biochemical and physical markers of localised inflammation correlate well with the extent of active synovitis (measured by contrast enhanced MRI).

2. Methods

2.1 Participants

474 Participants aged 50-79 years with symptomatic, radiographic KOA, and pain in the knee for most days in the last month were enrolled in the Vitamin D Evaluation in Osteoarthritis (VIDEO ISRCTN94818153) trial; a double-blind, 1:1 randomized placebo controlled trial investigating the impact of vitamin D supplementation on the progression of KOA. Daily supplementation with 800 IU cholecalciferol did not slow the rate of radiological progression or lead to symptoms reduction (24). For those participants with bilateral radiographic KOA the participant was asked which knee was most symptomatic and this was used in analysis. For this substudy participants at one of the five VIDEO recruiting centres (Southampton, N=152) were included.

2.2 MRI Acquisition

MRI of the index knee was performed on a single occasion in each participant on a 1.5T Signa MRI system (GE Healthcare, Milwaukee, USA) utilising a dedicated phased array knee coil. The following pulse sequence protocols were used for the present study:the axial and sagittal T1-w fs CE (TR 620 ms, TE 15.8 ms, slice thickness/slice gap 4.0 mm/0.2 mm, echo train length 2, field of view 16.0 x 16.0 cm, matrix size 256 x 160, number of signal averages 2) sequences. The contrast-enhanced scans were acquired beginning 3 minutes after intra-venous injection of 0.2 ml (0.1mmol)/kg body weight Gadodiamide (Omniscan^{TM}, GE Healthcare, Little Chalfont, UK). As both CE sequences required around 4 min scan time, image acquisition of the CE sequences was performed between 3 and 11 minutes after i.v. contrast injection. Image assessment of enhancement was performed weeks to months after the images were acquired.

2.3 MRI Interpretation

Synovitis was scored semi-quantitatively (graded 0 to 3), using a validated scoring system(25), at 11 anatomical sites (see supplementary file Table S4). The reading was performed by one musculoskeletal radiologist with 8 years' experience in standardised semi-quantitative assessment of knee OA (FWR). The reported intra-reader reliability originally performed on 50 knees by the same expert reader used in the present study and a second expert musculoskeletal radiologist who is a co-author (AG) ranges from 0.67 to 1.00 for the 11 sites.

2.4 Outcomes

Patient self-reported pain was assessed using the WOMAC pain subscale (range 0 to 100, 0 = no pain, 100 = extreme pain). Clinical outcomes included effusion (graded 0 to 3), warmth of the knee (any or none) and joint line tenderness (JLT) assessed by a trained clinical research nurse

(any or none; total, medial and lateral). Erythrocyte sedimentation rate (ESR) was used as a biochemical measure of inflammation, whilst Kellgren and Lawrence (KL) grade was used as a radiographic measure of structural osteoarthritis severity. Functional outcomes were time taken to walk 10 metres and peak supine quadriceps force (SQF) and patient self-reported WOMAC stiffness score (range 0 to 100, 0 = no disability, 100 = extreme disability). Where possible, outcomes were obtained on the day of the MRI. When outcome data were not available for this date, measures from the VIDEO trial visit closest to the MRI were used.

2.5 Statistical Analysis

An overall synovitis score was calculated for each participant as the cumulative number of regions with a synovitis grade $\geq$1. A binary synovitis indicator variable, equal to 1 if the sum of the 11 regional scores was greater than the median overall synovitis score (patient in the top 50%) was also generated. Secondary scores included only regions affected in (i) the medial area (peripatellar medial and perimeniscal medial) or (ii) the lateral area (peripatellar lateral and perimeniscal lateral). The synovitis grades for each of the two regions within each area were summed to create medial and lateral scores ranging from 0 to 6 and increase power to detect differences between these two regions.

Multiple linear regression models were used to assess the associations between synovitis and the numerical outcomes of interest (WOMAC scores, 10m walk time, peak SQF and ESR). Log-binomial regression models were used to assess the associations between synovitis and the binary outcome variables of interest (Warmth and JLT) and ordinal logistic regression models were used when the outcome was ordinal (Effusion and KL grade). All regression models were adjusted for the same set of potential confounders: age, gender, body mass index (BMI), the presence of Heberden's nodes and whether the patient had been randomised to receive vitamin D supplementation in the VIDEO trial.

To assess whether the association of synovitis with WOMAC pain was independent of KL grade, further adjustment for KL grade was made within the analysis model. Where the effect size for synovitis remained substantially unchanged or statistically significant, synovitis was assumed to

have an association with the outcome at least partially independent of KL grade. The Bayesian Information Criteria (BIC) was used to compare models investigating whether synovitis or KL grade was most strongly associated with pain. The best model has the minimum value of BIC. A reduction in BIC of 2-6 indicates positive evidence for the simpler model, 6-10 indicates strong evidence and reductions >10 provide very strong evidence for the simpler model(26).

Southampton VIDEO participants with a complete set of synovitis scores (for all 11 anatomical sites) were included in the analysis. Selection bias was investigated by comparing the baseline clinical characteristics of those included and excluded from the analysis due to incomplete data. For normally distributed continuous data, the two-tailed unpaired t-test was used for comparisons. For non-normal continuous data the Mann-Whitney U test was used. All statistical analysis was performed using Stata/IC version 11.2, (StataCorp, College Station, TX, USA).

3. Results

3.1 Outcome Data

107 patients satisfied the inclusion criteria of complete MRI and clinical data. There were no substantial or significant differences in baseline characteristics between those individuals included in the study and those excluded due to incomplete synovitis data (data not shown). MRI examination was performed at the baseline VIDEO visit for 43 (40%) patients; at the 12 month visit for 35 (33%) patients; at the 24 month visit for 27 (25%) patients and at the 36 month visit for 2 (2%) of the included patients. WOMAC pain scores were obtained on the date of MRI for all patients except one, whose score was obtained at the subsequent VIDEO trial visit (6 months post MRI). Table 1 summarises the time between MRI acquisition and outcome assessments.

3.2 Patient Characteristics

Of those subjects included, 64% were female, with an average age of 65 years and average BMI of 29kg/m^2. 53% were allocated to receive vitamin D supplementation. The median number of regions with evidence of synovitis was 9 (range 2 to 11). Demographic, clinical and

inflammatory patient characteristics are compared between those with <9 and ≥9 regions with evidence of synovitis in Table 2. Patients with a greater number of regions affected by synovitis had higher WOMAC pain scores, were more likely to have Heberden's nodes, older, with higher ESR and higher KL grades. In contrast, JLT was more common amongst those subjects with fewer regions affected by synovitis (58% versus 37%). Joint effusion was more common in subjects with a greater extent of synovitis.

3.3 Total Synovitis

The association between the total number of regions affected by synovitis and each of the outcome measures is summarised in Table 3. A significant association was observed between extent of synovitis and the WOMAC pain score. For each additional region affected with synovitis there was a 1.82 average increase in WOMAC pain score (95% CI 0.05 to 3.58; p=0.04). There was no statistically significant evidence for an association between synovitis and the WOMAC stiffness score.

Synovitis was significantly negatively associated with JLT with a relative risk (RR) of 0.87 (95% CI 0.84 to 0.90; p<0.01) for each additional region affected by synovitis. Conversely synovitis was positively associated with effusion. For each additional region affected by synovitis the odds that a patient has a higher effusion grade increases 1.69 times (95% CI 1.37 to 2.08, p<0.01). There was no evidence of a significant relationship between warmth and the extent of synovitis, however there was limited power to detect differences due to the low number of patients presenting with warmth (n=3).

A significant association was observed between evidence of synovitis and radiographic severity as measured using the KL grading system (p<0.01) (Table 3). For each additional region affected by synovitis, the odds that a patient has a higher KL grade increases 1.50 times (OR = 1.50; 95% CI 1.23 to 1.76; p<0.01).

Adjustment of the WOMAC pain model for KL grade indicates that the association observed between WOMAC pain and synovitis may not be independent of KL grade (Table 4). The effect size attributable to an additional synovitis region after adjustment for KL grade is an increase of 1.32 in WOMAC Pain score, and no longer statistically significant (p=0.18). The strong correlation between KL grade and synovitis led to issues of collinearity. Using Bayesian information criterion (BIC) as a model selection criteria there is strong evidence the synovitis score is better at predicting WOMAC pain than KL grade (BIC=965.50 versus BIC= 971.58). The inclusion of both variables did not improve the fit of the model (BIC=974.24). There was no evidence of an interaction between KL grade and synovitis (p=0.62).

There was no evidence of any association between the extent of synovitis and ESR, walk time or quadriceps strength (Table 3).

3.4 Binary Synovitis Indicator

A significant relationship between synovitis considered as a binary variable (number of regions with synovitis <9 or ≥9) and pain, as measured by the WOMAC pain score was observed. A significant association was also found between synovitis (<9 or ≥9) and the KL grade (results not shown).

Synovitis (<9 or ≥9) remained a significant predictor (p=0.02) after adjustment for KL grade (Table 5). There was no longer a significant relationship between KL grade and pain, when synovitis (<9 or ≥9) was included in the model.

A comparison of results in Table 5 with adjustment for KL grade to those in Table 4, indicates that the model with synovitis as a binary predictor (BIC = 970.60) provides a better fit for pain than synovitis treated as a numerical variable (BIC = 974.24). The number of regions with synovitis <9 or ≥9, without adjustment for KL grade, is the best predictor of WOMAC pain, BIC=961.03.

3.5 Medial and Lateral Synovitis

The median sum of the synovitis grades from the two medial regions (peripatellar medial and perimeniscal medial) was 3, range 0 to 5. The extent of lateral synovitis (peripatellar lateral, perimeniscal lateral) was slightly lower with a median score of 2, range 0 to 6.

The relationship between extent of medial synovitis and WOMAC pain score was strongly positive with an average 3.21 (95% CI 0.43 to 5.99; p=0.02) point increase in pain score for an increase in synovitis grade in a single medial region. This effect size is substantially larger than that observed between the total number of regions with synovitis and WOMAC pain (Table 3). There was no significant relationship between the extent of lateral synovitis and the WOMAC pain score (1.87; 95% CI -0.72 to 4.46; p=0.16) (Table 6).

3.6 Sensitivity Analyses

Only 9 patients with KL Grade 4 were included in analysis, of which only 2 had <9 regions with synovitis (Table 2). Sensitivity analysis excluding these 9 patients showed a strong positive association between WOMAC pain and synovitis. All other results similarly remained consistent in sensitivity analysis (see supplementary file Table S1 to S3).

ESR fluctuates over time and 55 (51%) participants had ESR tested on the date of MRI. Sensitivity analysis was performed in this group and confirmed no evidence of association between ESR and synovitis (0.96, 95% CI 0.85 to 1.07, p=0.512).

4. Discussion

The findings of this study suggest that there is a strong association between the number of regions affected by synovitis and WOMAC pain. Regression models predicting pain from both extent of synovitis and KL grade indicated that the best model only included whether or not there was synovitis in ≥9 regions. There is also evidence that medial synovitis is more strongly associated with pain than lateral synovitis.

Other significant associations found were a positive relationship between effusion and synovitis, and a negative association between the extent of synovitis and JLT. The strong positive relationship between synovitis and effusion has previously been observed (27) and is not unexpected since inflammation of the synovial membrane is frequently accompanied by effusion into the synovial sac. The effusion measure may therefore simply be measuring one component of the synovitis itself. Further it has been noted that effusion measured from PD FS MRI may be measuring both joint effusion and synovial thickening and thus effusion may be overestimated (27, 28) which may contribute to the strong associations observed between these two measures.

The strong positive association identified between the number of regions affected by synovitis and KL grade is consistent with previous studies (29). However, in recent years there has been a growing acceptance that KL grade does not correlate well with patient experience of pain. Some researchers report a threshold effect whereby a small radiographic change is associated with substantially increased pain, however further damage does not always appear associated with reports of increased pain (30). Previous study of participants with no radiographic osteoarthritis found no association between experience of pain, aching or stiffness in the previous month and the presence of synovitis(31). However a systematic review of studies of osteoarthritis patients did find evidence of a positive association between pain and synovitis (32), and this was further supported by the findings of a general population study of middle-aged women (33). The contrast in these findings is particularly interesting in the context of the current study where, whilst both synovitis and KL grade are strong predictors of WOMAC pain scores, they are not independent predictors, with the extent of synovitis explaining little additional variability in pain compared to KL grade alone. The association between synovitis and WOMAC pain in this study does therefore appear to be at least partially mediated by KL grade. The high correlation between KL grade and synovitis has been noted previously (33, 34). When using BIC as a model selection criteria, synovitis provides a better model for WOMAC pain

scores than does KL grade, suggesting that synovitis might more reliably identify patients with more painful symptoms. The greater granularity with which synovitis was measured (on a scale of 0 to 11) compared to KL scale (on a scale of 0 to 4) needs to be considered and is a possible explanation for this finding. That said, in the context of the existing literature these findings do support the need for further research into understanding possible interactions between KL grade and synovitis in the context of knee pain. Such a study should ideally consider participants with KL grades ranging from 0 to 4.

This study also investigated whether medial or lateral synovitis was more strongly associated with knee pain. The association between the extent of medial synovitis and WOMAC pain score was strong and suggests that inflammation of the synovial membrane in medial regions may be a mediator of pain in osteoarthritis. In contrast the association between synovitis in the lateral region and WOMAC pain was not statistically significant. However the odds ratio of 1.87 does suggest that lateral synovitis may still be an important factor in explaining pain in osteoarthritis. The possibility that medial synovitis may have a greater role in explaining knee pain than lateral synovitis has been suggested previously [26]. Research indicates that knee osteoarthritis is more commonly a disease of the medial compartment [27]. The high correlations between KL grade and synovitis [24] would therefore lead to an expectation that higher levels of medial synovitis would be observed in this (at least equivocal) knee osteoarthritis cohort. In the current study the median number of medial regions affected is 3 compared to a median of 2 lateral regions. However the numbers of participants with any medial or any lateral synovitis are very similar (93% versus 91%). Higher prevalence of medial synovitis therefore appears to be an unlikely explanation for the finding. It is widely believed that patients with medial knee osteoarthritis are more likely to experience painful symptoms. Whilst we are not aware of any published study confirming this anecdotal opinion, the current study supports the idea that the medial compartment may be more important in determining pain. Further research is required to establish whether medial synovitis is influencing any association between medial disease and pain.

The negative association of synovitis with JLT warrants more consideration. The consistency of the associations between any, medial or lateral synovitis with any, medial or lateral JLT provides further confirmation of the observed association. However, it is acknowledged that this finding contrasts with previous literature which suggests that JLT may be one of the symptoms indicative of synovitis. This might indicate that synovitis ascertained through MRI is a distinct phenomenon from that measured by traditional methods. Nevertheless, a recent study found a strong positive association between MRI measured medial synovitis and medial JLT and no association between lateral symptoms in the knees of patients with OA (35). The association between JLT and synovitis in patients with painful OA is an area for further investigation.

The use of gadolinium enhanced MRI to accurately assess synovitis and the detailed nature of the clinical assessments provide this study with substantial strengths. However, there are several limitations of this study. Aside from the widely accepted limitations of using data from trials in terms of generalisability, the sample size is low. There was a high level of exclusion, since almost one third of Southampton VIDEO patients did not have complete synovitis data. However many of the participants were excluded due to having no contrast enhanced MRI sequences or having partial sequences and therefore can be considered to be missing completely at random. Statistical analysis found no significant differences in the baseline characteristics of those included and excluded from the analysis. A further limitation is the discord between the date of MRI assessment of synovitis and effusion, and the date of assessment of other clinical and functional outcomes in some patients. However this affected only 20% of outcome measures, and only 1 single measure of WOMAC pain and stiffness was from a different visit date (within 6 months). Finally, with only limited adjustment for potential confounding there is the possibility of residual confounding, particularly in the association between synovitis and pain which is known to be confounded by multiple factors. Adjustment for further factors such as psychological measures of depression may be warranted in future studies.

5 Conclusion

The current study indicates that there is a strong positive association between medial

compartment synovitis and pain as measured by the WOMAC questionnaire. Clinically detectable effusion is also positively associated with synovitis. Non-operative treatments directed at management of inflammation and future trials targeting the synovial tissue for treating KOA should consider these two factors.

Author Contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version. Prof. Arden had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1 – Time (in months) Between MRI and Outcome Assessments

Outcome	Recorded on date of MRI N (%)	Time between MRI and outcome assessment Median (Range)
KL grade	107 (100%)	0
JLT	107 (100%)	0
Effusion	107 (100%)	0
WOMAC (Pain, Stiffness)	106 (99%)	0 (0 to 6)
Warmth	101 (94%)	0 (0 to 24)
10m Walk Time	80 (75%)	0 (0 to 12)
Peak SQF	79 (74%)	0 (0 to 12)
ESR	55 (51%)	0 (0 to 24)

Table 2 –Demographic and Clinical Characteristics of Study Participants

Baseline		<9 regions with evidence of synovitis N=48	≥9 regions with evidence of synovitis N=59	p-value
Age[1]	(years)	62 (8)	67(8)	0.01
Gender[2]	(male)	21 (44%)	18 (31%)	0.16
	(female)	27 (56%)	41 (69%)	
BMI[1]	(kg/m^2)	28 (4)	29 (5)	0.43
Heberden's Nodes[2]	(present)	34 (71%)	49 (83%)	0.13
Vitamin D (VIDEO intervention)	(allocated)	28 (58%)	29 (49%)	0.34
Vitamin D_3	(μg/L)	20.6 (9.9)	22.8 (8.5)	0.21
Analgesics	(taking)	21 (44%)	26 (44%)	0.97
ESR[3]	(mm/hr)	2 (0 to 4)	3 (0 to 9)	0.04
Warmth[2]	(present)	1 (2%)	2 (3%)	0.68
JLT[2]	(present)	28 (58%)	22 (37%)	0.11
WOMAC Stiffness[1,4]	(score)	39 (24)	48 (26)	0.09
WOMAC Pain[1,4]	(score)	27 (19)	37 (21)	0.01
Effusion[2]	0	22 (46%)	7 (12%)	<0.01
	1	17 (35%)	19 (32%)	
	2	8 (17%)	26 (44%)	
	3	1 (2%)	7 (12%)	
10m Walk Time[3]	(seconds)	8 (7 to 10)	8 (7 to 10)	0.46
Peak SQF[3]	(kg)	12 (8 to 16)	10 (5 to 14)	0.08
KL Grade[2]	1	15 (31%)	2 (3%)	<0.01
	2	20 (42%)	21 (36%)	
	3	11 (23%)	29 (49%)	
	4	2 (4%)	7 (12%)	

Data is presented as [1]mean (standard deviation) for normally distributed variables, [2]N (%) for categorical variables and [3]median (interquartile range) for non-normally distributed variables. [4] WOMAC scores range 0 to 100;0 = no pain/disability, 100 = extreme pain/disability.

Table 3 –Association Between Total Number of Regions with Synovitis and Each Outcome Measure (N=107)

Outcome	Absolute Effect[1,2]	95% CI	p-value
WOMAC Pain	1.82	0.05 to 3.58	0.04
WOMAC Stiffness	1.57	-0.66 to 3.81	0.17
	Relative Effect[1,3]	95% CI	p-value
10m Walk Time (seconds)	0.99	0.97 to 1.02	0.73
Peak SQF (kg)	0.99	0.95 to 1.04	0.72
ESR (mm/hr)	0.99	0.92 to 1.06	0.67
	Relative Risk[1,4]	95% CI	p-value
Warmth	1.49	0.69 to 3.24	0.31
JLT	0.87	0.84 to 0.90	<0.01
	Odds Ratio[1,5]	95% CI	p-value
Effusion	1.69	1.37 to 2.08	<0.01
KL Grade	1.50	1.23 to 1.76	<0.01

[1]All regression models are adjusted for age, gender, BMI, presence of Heberden's nodes and VIDEO trial arm.
[2]Absolute effects from linear regression models refer to the increase in the associated outcome variable for one further region having evidence of synovitis
[3]Relative effects from linear regression models where natural log transformation of the outcome was required refer to the relative change in the original untransformed outcome variable for one further region having evidence of synovitis. Due to the non-linearity in the relationship between synovitis and ESR, time taken to walk 10 metres and peak supine quadriceps force (SQF), the dependent variables were natural log transformed.
[4]Relative Risks from log binomial regression models refer to the proportional risk of the associated outcome for one further region having evidence of synovitis
[5]Ordinal regression odds ratios refer to the odds of a higher associated outcome category for one further region having evidence of synovitis

Table 4 – Association Between Total Number of Regions with Synovitis and WOMAC Pain Score After Adjusting for KL grade (N=107)

WOMAC Pain		Absolute Effect[1,2]	95% CI	p-value	Test for trend
Synovitis		1.32	-0.61 to 3.25	0.18	
KL Grade	1	Baseline			
	2	6.23	-5.58 to 18.03	0.30	0.12
	3	4.93	-7.51 to 17.38	0.43	
	4	18.31	1.27 to 35.35	0.04	

[1]Absolute effect sizes are adjusted for age, gender, BMI presence of Heberden's nodes and VIDEO trial arm.
[2]Absolute effects sizes from the linear regression model refer to the increase in WOMAC pain score for one further region having evidence of synovitis

Table 5 – Association Between Total Number of Regions with Synovitis Categorised into a Binary Score (<9, ≥9 regions) and WOMAC Pain Score (N=107)

WOMAC Pain		Absolute Effect[1,2]	95% CI	p-value	Test for trend
Model without KL Grade:					
Synovitis	≥9 regions	11.69	3.79 to 19.58	<0.01	
Model with KL Grade:					
Synovitis	≥9 regions	9.96	1.34 to 18.58	0.02	
KL Grade	1	Baseline			
	2	4.16	-7.66 to 15.98	0.49	0.21
	3	2.54	-9.81 to 14.90	0.68	
	4	15.72	-1.07 to 32.51	0.07	

[1]Absolute effect sizes are adjusted for age, gender, BMI presence of Heberden's nodes and VIDEO trial arm.
[2]Absolute effects sizes from the linear regression model refer to the increase in WOMAC pain score when ≥9 regions have evidence of synovitis

Table 6 –Association Between Sum of Synovitis Grades Across the Medial and Lateral Regions and Outcome Measures (N=107 except JLT lateral where N=106)

		Medial			Lateral	
Outcome	Absolute Effect[1,2]	95% CI	p-value	Absolute Effect[1,2]	95% CI	p-value
WOMAC Pain	3.21	0.43 to 5.99	0.02	1.87	-0.72 to 4.46	0.16
WOMAC Stiffness	3.02	-0.50 to 6.55	0.09	2.77	-0.46 to 6.01	0.09
	Relative Effect[1,3]	95% CI	p-value	Relative Effect[1,3]	95% CI	p-value
10m Walk Time (seconds)	0.90	0.94 to 1.03	0.53	0.97	0.93 to 1.01	0.15
Peak SQF (kg)	0.96	0.89 to 1.03	0.23	0.97	0.91 to 1.04	0.45
ESR (mm/hr)	0.95	0.85 to 1.06	0.40	1.01	0.91 to 1.10	0.91
	Relative Risk[1,4]	95% CI	p-value	Relative Risk[1,4]	95% CI	p-value
Warmth	2.05	0.69 to 6.05	0.19	1.97	0.80 to 4.87	0.14
JLT Any	0.82	0.71 to 0.95	0.01	0.83	0.72 to 0.96	0.61
Medial	0.82	0.69 to 0.98	0.03	0.80	0.67 to 0.95	0.01
Lateral	0.81	0.65 to 1.01	0.06	0.82	0.67 to 0.99	0.04
	Odds Ratio[1,5]	95% CI	p-value	Odds Ratio[1,5]	95% CI	p-value
Effusion	1.87	1.41 to 2.48	<0.01	2.14	1.62 to 2.83	<0.01
KL Grade	1.77	1.33 to 2.35	<0.01	1.83	1.40 to 2.40	<0.01

[1]All regression models are adjusted for age, gender, BMI, presence of Heberden's nodes and VIDEO trial arm.
[2]Absolute effects from linear regression models refer to the increase in the associated outcome variable for a one point increase in synovitis grading
[3]Relative effects from linear regression models where natural log transformation of the outcome was required refer to the relative change in the original untransformed outcome variable for a one point increase in synovitis grading
[4]Relative Risks from log binomial regression models refer to the proportional risk of the associated outcome for a one point increase in synovitis grading
[5]Ordinal regression Odds Ratios refer to the odds of a higher associated outcome category for a one point increase in synovitis grading