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Synovial pathology detected on ultrasound correlates with the severity of radiographic knee osteoarthritis more than with symptoms

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ABSTRACT

Objective: To [1] compare the frequency and severity of ultrasound (US) features in people with normal knees (controls), knee pain (KP), asymptomatic OA (ROA), and symptomatic OA (SROA), [2] examine relationships between US features, knee pain, radiographic OA, [3] explore the relationship between change in pain and US features over a 3-month period.

Method: Community participants were recruited into a multiple group case-control study. All underwent assessment for pain, knee radiographs and US examination for effusion, synovial hypertrophy, popliteal cysts and power Doppler (PD) signal within the synovium. A 3-month follow-up was undertaken in over half of control and SROA participants.

Results: 243 participants were recruited (90 controls; 59 KP; 32 ROA; 62 SROA). Effusion and synovial hypertrophy were more common in ROA and SROA participants. Severity of effusion and synovial hypertrophy were greater in SROA compared to ROA (p<0.05). Severity of US effusion and synovial hypertrophy were correlated with radiographic severity (r=0.6 and r=0.7, p<0.01) but the relationship between pain severity and US features was weak (r=0.3, p<0.01). In SROA participants, knee pain did not change in tandem with a change in synovial hypertrophy over time.

Conclusion: US abnormalities are common in OA. Effusion and synovial hypertrophy were moderately correlated with radiographic severity but the relationship with pain is less strong. The degree to which these features reflect “active inflammation” is questionable and they may be better considered as part of the total organ pathology in OA. Further studies are warranted to confirm these findings.
Introduction

Pain is the major stimulus for people with knee osteoarthritis (OA) to seek medical attention but the causes of pain are complex and radiographs which are the standard for clinical imaging in OA are often discordant with symptoms\textsuperscript{1, 2}. In recent years there has been increasing interest in the role of the synovium in painful OA. Although nowhere as florid or extensive as the inflammation observed in rheumatoid arthritis, clinical effusions and capsular thickening can be clinically evident in some joints with knee OA, and are more frequently observed using sensitive measures such as ultrasound (US) and MRI\textsuperscript{3-10}. Synovial changes in OA are regarded by many as a secondary response to the degradation of cartilage\textsuperscript{11} though there are others who advocate them as a primary driver for OA which may be partly responsible for pain and disease progression\textsuperscript{12-16}.

Ultrasound (US) allows the direct and indirect evaluation of synovial abnormalities, namely the presence of grey scale features (effusion, synovial hypertrophy and bursitis) which are widely considered to be features of inflammation in OA. In addition the presence of increased power Doppler signal (PDS) within the synovium is purported to represent more active inflammation\textsuperscript{17}. Synovial abnormalities are more common in those with painful knee OA compared to those with asymptomatic OA or normal knees but the association between individual US features and pain is not conclusive\textsuperscript{6, 9, 10, 18-20}. Indeed, no single US feature has been consistently associated with knee pain and it has been suggested that the presence of effusion and synovial hypertrophy may be a marker for structural damage as opposed to inflammation\textsuperscript{4, 21}. Additionally, most US studies have been conducted in secondary
care settings and the same may not apply to people with knee OA in primary care where the vast majority of patients are managed.

The primary aim of this study was to compare the frequency and severity of synovial abnormalities in people with normal knees, knee pain, radiographic OA and symptomatic OA from the community. Secondary aims were to examine the relationships between US features, pain and radiographic severity and to observe whether temporal change in knee pain over a 3-month period correlated with a change in US findings.

**Methods**

A case-control design was used to compare 4 groups: people with normal knees (controls - without pain and without radiographic OA), knee pain without radiographic OA (KP), asymptomatic radiographic OA (ROA) and symptomatic ROA (SROA). Knee pain was classified according to the worst item score on any of the five WOMAC pain items. Those reporting at least moderate pain were classified as pain positive and those reporting none or mild pain were classified as pain negative. Radiographic OA was defined as Kellgren & Lawrence (K/L) grade ≥2. 

Participants were recruited from previous community studies of knee pain or knee OA (as either cases or controls) where they had consented to being approached for future research. The primary source of study participants was a cohort study of incident knee pain in the community. Additional participants were recruited from a randomised controlled trial of non-prescription analgesics for people with chronic
knee pain and a population based case-control study (Genetics of OA and Lifestyle (GOAL) study. Participants were purposefully recruited with the aim of attaining fifty participants in each of the four comparison groups. Sample size was based on a best estimate from the limited published data for prevalence of knee effusion for each group. Assuming a prevalence of 60% in the SROA group, 30% in the KP and ROA group and 5% in the control group, 50 participants were required in each group (200 in total) to detect the minimum difference between groups with 90% power and <5% type 1 errors. Control and SROA participants were invited to attend a follow-up US and pain assessment at 3 months.

Participants were excluded if they had a clinical history of inflammatory arthritis, clinical hip OA, knee joint replacement, knee joint injury or surgery in the previous 3 months, steroid injection to either knee in the previous 3 months, a diagnosis of Fibromyalgia or chronic widespread pain or severely impaired mobility (Steinbrocker Grade IV). Participants were asked to refrain from taking any non-steroidal anti-inflammatory drugs (NSAID) for 48 hours prior to the assessment to allow an adequate wash-out period; paracetamol could be taken for rescue pain-relief up to 12 hours before.

Study approval was granted by the Derbyshire Research Ethics Committee and all participants gave written informed consent. All participants underwent a clinical assessment, US and radiographic evaluation between April 2010 and March 2012.

Assessments
A range of data was collected including age, gender, body mass index (BMI), duration of early morning stiffness (EMS) (minutes) and the presence of a moderate clinical knee effusion. The Western Ontario and McMaster Osteoarthritis Index (WOMAC) was also used to evaluate knee stiffness and function\textsuperscript{26}.

Pain was assessed using 3 measures, a visual analogue scale (VAS) from 0-100mm for current knee pain severity, the pain subscale of the WOMAC questionnaire\textsuperscript{26} and the Measure of Intermittent and Constant Osteoarthritis Pain questionnaire (ICOAP)\textsuperscript{27}.

Standardised, weight-bearing, semi-flexed tibio-femoral and skyline 30\degree patello-femoral radiographs were scored by a single reader (SD) who was blinded to US features and pain. Radiographs were scored using the Nottingham logically derived Line Drawing Atlas (LDA)\textsuperscript{28, 29}. This scoring system uses mathematically calculated intervals for grading joint space width (JSW) and size of osteophyte for all three compartments of the knee, to produce an ordinal summated score. Intra-observer reproducibility for scoring using the LDA has been established as good (kappa = 0.82 (95\%, CI 0.78-.089) for JSW and 0.68 (95\% CI, 0.63-0.71) for size of osteophyte)\textsuperscript{28}. An overall Kellgren & Lawrence (K&L) grade (0-4) was also given to each knee.

**Ultrasound assessment**

US was performed by a single assessor (MH) on the same day as clinical assessments using a Toshiba Aplio SSA-770A machine with a multi-frequency (7-12 MHz) linear array transducer. The assessor was blind to the radiographic scores but not the clinical findings.
A standardised protocol reflecting current definitions and guidelines was followed\textsuperscript{5, 30}. Knees were scanned in longitudinal and transverse planes with the joint supported in 30° flexion for ventral and lateral scans and in extension for dorsal scans. The supra-patellar pouch was scanned widely (including the lateral and medial recesses). The following features and measurements were recorded:

1. **Effusion**: maximal depth was measured in mm and dichotomised as absent if < 4mm and present if ≥ 4mm\textsuperscript{5}.

2. **Synovial hypertrophy**: maximal depth was measured in mm and dichotomised as absent if < 4mm and present if ≥ 4mm\textsuperscript{5}.

3. **Baker’s cyst**: the diameter was measured in the transverse plane and dichotomised as absent if <4mm or present if ≥ 4mm\textsuperscript{10}.

4. **Bursitis**: bursae at the infra-patellar tendon and the insertion of the pes-anserinus site were measured and dichotomised as absent if <4mm or present if ≥ 4mm infra-patellar bursae, and absent if <2mm or present if ≥ 2mm for the pes-anserine bursa\textsuperscript{10}.

5. **Power Doppler Signal**: areas of hypertrophic synovium were scanned A pulse repetition frequency of 1000-1300Hz with a medium wall filter was used and the gain was adjusted so the background signal was removed. Increased signal was observed in both longitudinal and transverse planes and was scored using a semi-quantitative system grade 0-3, (0=absent, 1=mild, 2=moderate, 3= marked or severe)\textsuperscript{7}.

Intra-observer reliability for US measures was tested by performing a second scan within 1 week on 28 knees by the same assessor (MH). Intra-class correlation coefficients (ICC) were calculated for continuous measures of effusion 0.93 (95% CI, 0.75-0.98), synovial hypertrophy 0.89 (95% CI, 0.64-0.97) and popliteal cysts 0.79.
Intra-observer reliability for PDS was evaluated using a weighted kappa and was statistically perfect, kappa = 1.0 (p<0.001), but will have been influence by the low occurrence of PDS.

**Statistical analysis**

Our primary analysis was to compare the differences between groups. Analyses were carried out on data for the index knee (the most symptomatic, or randomly chosen knee) using IBM SPSS Statistics 19. All analyses were tested at the significance level p<0.05. For nominal or frequency data the Chi-square test was used, Fisher’s exact test was reported where the expected frequencies were less than 5. Post-hoc comparisons were made using the z-test with adjusted p values (the Bonferroni method was used when making multiple paired comparisons to control for Type I error rates). The distributions of continuous variables were tested using the Kolmogorov-Smirnov test. Differences between groups were then compared using the one-way ANOVA and post-hoc Bonferroni tests for normally distributed data and the Kruskal-Wallis test and post-hoc Mann Whitney tests with a Bonferroni correction for non-normally distributed data.

Secondary analysis examined the relationships between continuous US measures, pain VAS scores and radiographic severity (Nottingham LDA scores) using Pearson’s correlation coefficients or Spearman’s rho. Change in pain VAS scores and US measures at 3 month follow-up was examined using a paired t-test or Wilcoxon Signed Ranks Test, and correlation analysis was used to examine relationships between change in pain severity and change in US measures.
Results

Characteristics of study groups

Baseline assessments were performed on 243 participants, 65% were women, mean age was 70 years and BMI was 28.1 kg/m\(^2\). The four study groups were made up of 90 controls, 59 KP, 32 ROA, and 62 SROA participants. Recruited participants were representative of their original studies in terms of age though more females than males were recruited. Final recruitment to each group was unbalanced, with the ROA group under represented and SOA group over represented in the final analysis.

Baseline characteristics for each group are presented in table I. The gender distribution between each group was similar but the KP group was younger (p<0.05) and the control group had a lower BMI (p<0.05) compared to other groups. Pain variables did not differ between the KP and SROA groups. Radiographic severity (LDA scores) were higher in the SROA group compared to ROA group (p=0.05). Clinical effusions were rare among controls (2.2%) and KP participants (3.4%) but were more common in ROA (15.6%) (p<0.05) and again in SROA (50%), (p=0.05). Morning stiffness ≥ 30 minutes duration was exclusively reported by those with pain.

US findings at baseline

Table II summarises the US findings for each group. We found no difference in the frequency or severity of US features between control and KP participants. Effusions, synovial hypertrophy and popliteal cysts were more frequently observed in the ROA
and SROA groups compared to KP and control groups (p<0.05) (figure I). Synovial hypertrophy was more common again in the SROA compared to ROA group (p<0.05). The frequency of popliteal cysts increased in ROA (21.9%, p<0.05) and SROA (39%, p<0.05) groups compared to controls but were not different to each other. PD signal was more frequently observed in of SROA participants (16%) than control (2%, p<0.05) and KP (3%, p<0.05) groups. Grade of PD signal was not subject to analysis due to the low frequency observed. Infra-patellar bursae and pes-anserine bursae were rare and did not differ between groups.

Continuous measures of effusions and synovial hypertrophy were greater in ROA (mean depth (SD) = 6.0mm (2.8) and 3.9mm (3.9) respectively) compared to controls and KP groups (p<0.05), and were greater again in the SROA group (mean depth (SD) = 8.1mm (4.0) and 6.7mm (3.3), p<0.05 respectively) (figure II).

**Relationships between US features, pain and radiographic severity**

We found moderate correlations between radiographic scores derived from the LDA atlas and direct US measures of effusion and synovial hypertrophy (r= 0.6 and r=0.7 r=0.3 respectively, p ≤ 0.01) (table III). Correlations between pain VAS scores and US measures were weak but significant for effusion (r= 0.3, p<0.01) and synovial hypertrophy (r= 0.3, p<0.01) (table III). The strength of the correlation was similar for pain assessed using the VAS, WOMAC and ICOAP scores.

**Change in pain and US measures at 3 months**
At 3 months, follow-up assessments for pain and US measures were carried out in 45 (72.5%) of SROA participants and 57 (63%) of controls (table IV). Pain VAS scores and US measures did not change within the control group. In the SROA group, there was a statistically significant reduction in mean depth of synovial hypertrophy (mean difference= -1.4mm SD (3.0), p=0.003) after 3 months but there was no change in mean effusion, popliteal cyst measures or pain measures. We found no correlation between change in pain and change in US measures for either group (data not shown) though a change in US effusion was strongly correlated with a change in synovial hypertrophy that was statistically significant for both controls (r= 0.4, p<0.05) and SROA groups (r=0.6, p<0.01).

Discussion

This first community-based US study has confirmed that US features are more common in those with radiographic OA compared to those without and that severity of effusion and synovial hypertrophy are greater in those with painful OA. We found that direct measures of US features were moderately correlated with radiographic severity but had a weaker relationship with pain severity. Over a 3 month-period, SROA participants showed a reduction in mean synovial hypertrophy but there was no parallel reduction in knee pain suggesting that, in the community at least, US features accompany structural changes of knee OA but do not readily explain the severity of pain.

Previous studies have shown grey-scale US features to be common in SROA though prevalence rates vary between 33-86% for effusion and 17-93% for synovial...
hypertrophy\textsuperscript{5,8} and 6-43\% for popliteal cysts\textsuperscript{7,8}. Our frequency data are higher than some studies which may be attributable to variations in scanning protocols. We included the medial and lateral recesses of the supra-patellar pouch and joint lines when scanning and our findings are more comparable with those who scanned the joint widely\textsuperscript{8}. PD signal is frequently cited as a surrogate for active synovitis but is not commonly reported in US studies of knee OA\textsuperscript{6,32,33}. Our study is one of only a few that has reported using PDS and though we found it more frequently in SROA participants (16\%, p<0.05) compared to all other groups the severity was graded as only mild-moderate.

Few studies have directly investigated the relationship between radiographic severity and US features in knee OA. D’agostino et al reported the presence of greyscale US features was associated with higher radiological scores (K&L grade 3–4)\textsuperscript{5}, and MRI studies have also reported a significant relationship between synovial hypertrophy and radiographic severity\textsuperscript{34}. Using the Nottingham LDA we were able to correlate direct measures of US features with ordinal radiographic scores. We found moderate correlations between radiographic severity and US measures of synovial hypertrophy and effusion, which to us suggests that direct and indirect changes of the synovium are a reflection of the overall structural damage and reparative attempts of the osteoarthritic joint.

Previous conclusions on the relationship between US features and pain is knee OA are inconsistent. De Miguel et al reported US effusion to increase the risk of knee pain by 6.5 times and Baker’s cysts by 5.5 times but found no association between US features and pain severity\textsuperscript{10}. Others have reported positive associations between
US effusion with higher pain VAS scores on motion and at rest \textsuperscript{9,35}. However, two recent cross-sectional studies reported no association between US features and either the presence of knee pain or pain severity\textsuperscript{6,20}. We examined correlations between different pain measures (pain VAS, WOMAC, ICOAP intermittent and constant subscales) and direct measures of greyscale features and found that both effusions and synovial hypertrophy were both correlated with pain severity but only modestly so. There was also no difference between the strength of the relationship for intermittent knee pain and constant knee pain, which may be thought of as more mechanical and inflammatory type pain, respectively. Little has been reported on the temporal changes of US features relative to change in knee pain. MRI studies have shown that while an increase in synovitis correlates modestly with increased pain severity or more frequent pain, a reciprocal decrease is not observed when pain decreases\textsuperscript{36,37}. We found that in SROA participants mean measures of synovial hypertrophy decreased over a 3 month period but this was not accompanied by a parallel reduction in pain severity.

This suggests that perhaps synovial hypertrophy as observed on grey-scale US is not as “inflammatory” as we would like to believe. Previous studies have shown that grey-scale US cannot differentiate between synovial hypertrophy and synovitis, tissue debris and fibrosis are known to mimic some US features of synovial proliferation but these features do not exhibit PD signal \textsuperscript{38-40}. We found hypertrophy to be common but PD signal much less so. This raises the question that if effusion and synovial hypertrophy detected by US are not “inflammatory” in nature then what do they represent? The reduction in lymphatic vessels that occurs in knee OA synovium could cause increased synovial thickening and effusion through altered
dynamics of fluid drainage rather than from “inflammation”\textsuperscript{41}, and it has been suggested that altered joint biomechanics may permanently modify the baseline volume of synovial fluid\textsuperscript{42}. In knee OA, the precipitating event is almost always mechanical in nature resulting either from acute injury, repetitive micro-trauma, increased focal stresses from abnormal anatomy or a combination thereof \textsuperscript{11}. Capsular tissues are dynamic in terms of synthesis and orientation and respond to the biomechanical forces acting on them. Importantly, synovial thickening is localised rather than diffuse in OA and this may be reflective of damage in the adjacent areas of cartilage, bone or entheses but may also represent a cellular response to biomechanical stresses within the joint capsule. Different patterns of synovial thickening on US and MRI have been identified but whether they are associated with joint biomechanics has not yet been investigated \textsuperscript{8,43,44}. It seems likely from our data that effusion and synovial hypertrophy mainly reflect the overall changes that occur in knee OA.

There are some caveats to this study. Firstly, recruitment to the study was not random; participants were purposefully recruited to each study group with the aim of comparing four groups with a balanced number of 50 participants. Participants were drawn from previous community studies of knee pain for whom a variable amount of time (between 3 and 10 years) had passed between participation in the original and current study\textsuperscript{23-25}. As such, previous radiographic and pain status may have changed for some potential participants i.e. there would an incidence of new radiographic OA and new knee pain, as well as knee pain having resolved in others. The prevalence of asymptomatic ROA lies between 27-44% of the general population\textsuperscript{45} but identifying those participants is inherently difficult as they are asymptomatic and
require radiographs to confirm their status. Consequently, recruitment to each group was unbalanced, with the ROA group under represented and SOA group over represented in the final analysis. Secondly, the study design was primarily intended for the comparison of the 4 study groups. Secondary analyses examining the relationships between pain, structural change and US features were derived from the 4 different groups and the correlations may not be representative of the general population. Thirdly, the population for this study was drawn from the community and differences in population demographics limits direct comparisons with hospital-based US studies where SROA participants are often younger, with less severe radiographic changes but higher levels of reported pain\(^5\). Comparisons may also be limited by variations in definitions of US pathology and scanning protocols which vary between studies. Finally, issues around defining knee pain and knee OA are well documented\(^{46-49}\). We chose our defining criteria as it enabled all participants to be allocated to a group. As a consequence the comparison groups are not completely distinct, that is some control/ROA participants had mild symptoms and some control/KP participants had minor structural change (K&L grade1).

In conclusion, this study highlights the correlation between greyscale US features and radiographic severity. However, it questions the general assumption that synovial abnormalities are “inflammatory” in nature and is responsible for driving pain in OA, and suggests instead that they are a part of the overall structural pathology reflecting the biomechanical adaptations of the OA joint. PD signal which is widely asserted to represent a more “active inflammation” was more common in painful OA compared to controls but did not differ significantly from asymptomatic OA but this may not be the case for hospital referred patients. US features, particularly synovial
hypertrophy, may well have a role to play in the development of painful OA but given the multi-factorial nature of pain this is unlikely to be straightforward. Further longitudinal studies are required to demonstrate whether US features are important in the development and progression of structural change and symptoms.

**Contributions**

All authors were involved in drafting and critically reading the manuscript for important content and all authors approved the final version. MH had full access to the all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. MH, SD, PC, KL, WZ and MD.

Acquisition of data. MH, SD, KL

Analysis and interpretation of data. MH, SD, PC, KL, WZ and MD

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**Competing Interests**

All authors declare they have no competing interests

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Table I  Clinical characteristics of each group

| Characteristics                        | Controls (N=90) | KP (N=59) | ROA (N=32) | SROA (N=62) | P     |
|----------------------------------------|----------------|-----------|------------|-------------|-------|
| Age (years)                            | mean (SD)      | 71 (7.9)  | 63.8 (8.8)**| 73.1 (7.9)  | 73.9 (7.8) | <0.001|
| BMI (kg/m²)                            | mean (SD)      | 26.5 (4.4)**| 28.5 (4.0)  | 29.6 (5.3)  | 29.2 (4.1) | =0.001|
| Women                                  | n (%)          | 63 (70%)  | 33 (55.9%) | 19 (59.3%)  | 42 (67.7%) | =0.29 |
| Nottingham LDA scores                  |                |           |            |             |       |
| Global Score (0-60)                    | mean (SD)      | 1.1 (1.5) | 0.5 (1.1)  | 11.9 (7.1)* | 17.5 (8.0)** | <0.001|
| Pain characteristics                   |                |           |            |             |       |
| Pain VAS (mm)                          | mean (SD)      | 6.6 (11.0) | 48.9 (22.0)*| 7.2 (14.4)  | 48.2 (24.6)* | <0.001|
| WOMAC Pain (0-20)                      | mean (SD)      | 1.0 (1.51)| 8.0 (3.34)*| 0.9 (1.34)  | 8.1 (3.23)* | <0.001|
| ICOAP Subscales                        |                |           |            |             |       |
| Constant (0-20)                        | mean (SD)      | 0.5 (1.2) | 5.9 (4.8)* | 0.2 (.59)   | 6.9 (5.2)** | <0.001|
| Intermittent (0-24)                    | mean (SD)      | 1.6 (2.5) | 10.2 (4.1)*| 2.0 (3.1)   | 10.6 (5.5)** | <0.001|
| Clinical                               |                |           |            |             |       |
| Clinical effusion                      | n (%)          | 2 (2.2%)  | 2 (3.4%)   | 5 (15.6%)*  | 31 (50%)** | <0.001|
| EMS ≥30 mins                           | n (%)          | 0 (0%)    | 20 (37.7%)*| 0 (0%)      | 15 (27.3%)* | <0.001|
| WOMAC Stiffness (0-8)                  | mean (SD)      | 0.8 (1.1) | 3.4 (1.6)* | 0.9 (0.9)   | 4.0 (1.8)* | <0.001|
| WOMAC Function (0-68)                  | mean (SD)      | 4.2 (6.5) | 25.8 (12.3)*| 5.5 (6.6)   | 29.6 (11.8)* | <0.001|

*P value represents significant difference between the 4 groups using X² tests for frequency data and one-way ANOVA for continuous data.
*group differs significantly from control p<0.05 after applying post-hoc Bonferroni test
**group differs significantly from all groups p<0.05 after applying post-hoc Bonferroni test
KP, knee pain only; ROA, radiographic OA; SOA, symptomatic OA; BMI, Body Mass Index; LDA, line drawing atlas; WOMAC, Western Ontario and MacMasters Index; ICOAP, Intermittent and Constant Osteoarthritis Pain questionnaire; EMS ≥30 mins, a dichotomous variable was created for EMS (early morning stiffness) lasting longer than 30 minutes.
### Table II Frequency and severity of Ultrasound (US) features

| US Features                      | Controls (n=90) | KP (n=59) | ROA (n=32) | SROA (n=62) | p     |
|----------------------------------|----------------|-----------|------------|-------------|-------|
| Effusion n (%)                   | 26 (28.9)      | 19 (32.2) | 26 (81.3)* | 57 (91.9)*  | <0.001|
| Synovial hypertrophy n (%)       | 7 (7.8)        | 7 (11.9)  | 13 (40.6)* | 51 (82.3)**| <0.001|
| Popliteal cysts n (%)            | 11 (12.4)      | 5 (8.6)   | 7 (21.9)*  | 23 (39.2)*  | <0.001|
| Infra-pat bursitis n (%)         | 3 (3.3)        | 4 (6.8)   | 0 (0)      | 5 (8.1)     | 0.28  |
| Pes-Anserine Bursitis n (%)      | 0 (0)          | 0 (0)     | 0 (0)      | 4 (6.5)     | ns    |
| Power doppler signal n (%)       | 2 (2.2)        | 2 (3.4)   | 2 (6.3)    | 10 (16.2)*  | =0.005|
| Grade 1 n (%)                    | 2 (2.2)        | 1 (1.7)   | 2 (6.3)    | 5 (8.1)     |       |
| Grade 2 n (%)                    | 0 (0)          | 0 (0)     | 0 (0)      | 5 (8.1)     |       |
| Grade 3 n (%)                    | 0 (0)          | 1 (1.7)   | 0 (0)      | 0 (0)       |       |

**Continuous US features**

|                 | mean (SD) | mean (SD) | mean (SD) | mean (SD) | p     |
|-----------------|-----------|-----------|-----------|-----------|-------|
| Effusion (mm)   | 2.6 (2.7) | 3.4 (3.2) | 6.0 (2.8)*| 8.1 (4.0)**| <0.001|
| Synovial hypertrophy mean (SD) | 0.7 (1.5) | 1.0 (1.9) | 3.9 (3.9)*| 6.7 (3.3)**| <0.001|
| Popliteal cysts (mm) mean (SD) | 1.0 (2.6) | 0.8 (2.2) | 1.8 (3.6) | 3.5 (4.7)* | =0.001|

*P value represents significant difference between the 4 groups using $\chi^2$ tests for frequency data and one-way ANOVA for continuous data.

*differs significantly from control and KP group p<0.05
**differs significantly from all groups p<0.05

US, Ultrasound; KP, knee pain only; ROA, radiographic OA; SROA, symptomatic OA; BMI, Body Mass Index;
**Table III** Correlations between continuous US measures, pain severity and radiographic severity

|                          | Effusion (mm) | Synovial Hypertrophy (mm) | Popliteal cyst (mm) |
|--------------------------|---------------|----------------------------|---------------------|
| Pain VAS (mm)            | 0.3**         | 0.3**                      | 0.1                 |
| WOMAC pain subscale      | 0.3**         | 0.3**                      | 0.1                 |
| ICOAP Intermittent subscale | 0.3**       | 0.3**                      | 0.1                 |
| ICOAP Constant subscale  | 0.3**         | 0.3**                      | 0.1                 |
| Radiographic severity -  |               |                            |                     |
| Nottingham LDA score (0-60) | 0.6**        | 0.7**                      | 0.3**               |

** Correlation is significant at the 0.01 level

mm, millimeters; VAS, visual analogue scale; WOMAC, Western Ontario and MacMasters Index; ICOAP, Intermittent and Constant Osteoarthritis Pain questionnaire; LDA, Line Drawing Atlas
|                        | Controls N=57 |            | SROA N=45 |            |
|------------------------|---------------|------------|-----------|------------|
|                        | Baseline 3 months p | Baseline 3 months p |
| Pain VAS (mm)          | 3.1 (5.6) 5.8 (13.6) 0.33 | 52.5 (23.0) 54.0 (25.5) 0.65 |
| Effusion (mm)          | 2.3 (2.4) 2.2 (2.4) 0.80 | 8.6 (4.6) 8.6 (4.9) 0.96 |
| Synovial Hypertrophy (mm) | 0.6 (1.5) 0.7 (1.9) 0.67 | 7.1 (4.0) 5.7 (4.3) 0.003* |
| Popliteal cysts (mm) Median (range) | 0 (0-11.6) 0 (0-12.4) 0.53 | 0 (0-14.3) 1.15 (0.13.4) 0.45 |

Data represent mean (SD) unless stated. P value represents significant difference between the baseline and 3 months using paired t test for normally distributed and Wilcoxon signed rank test for non-normally distributed data. * difference is significant at <0.05

SROA, symptomatic OA; BMI, Body Mass Index; mm, millimeters
Figure I Bar chart showing frequency (%) of US features within each comparison group.

Figure II US measures of (A) effusion and (B) synovial hypertrophy for each group.