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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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SUMMARY

Objective: To [1] compare the frequency and severity of ultrasound (US) features in people with normal knees (controls), knee pain (KP), asymptomatic radiographic OA (ROA), and symptomatic OA (SROA), [2] examine relationships between US features, pain and radiographic severity, [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, pain severity 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[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[3–10]. Synovial changes in OA are regarded by many as a secondary response to the degradation of cartilage[11] though there are others who advocate them as a primary driver for OA which may be partly responsible for pain and disease progression[12–16].

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[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[6,9,10,18–20]. Indeed, no single US feature has been consistently

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associated with knee pain (KP) and it has been suggested that the presence of effusion and synovial hypertrophy may be a marker for structural damage as opposed to inflammation[4,5]. Additionally, most US studies have been conducted in secondary care settings and the same may not apply to people with knee OA in the community 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, KP, 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 pain severity over a 3-month period correlated with a change in US findings.

Methods

A case–control design was used to compare four groups: people with normal knees (controls – without pain and without radiographic OA), KP without radiographic OA, asymptomatic radiographic OA (ROA) and symptomatic ROA (SROA). KP was classified according to the worst item score on any of the five Western Ontario and McMaster Osteoarthritis Index (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[21].

Participants were recruited from previous community studies of KP 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 KP in the community[22]. Additional participants were recruited from a randomised controlled trial of non-prescription analgesics for people with chronic KP[23] and a population based case–control study (Genetics of OA and Lifestyle (GOAL)) study[24]. 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[5,9,10]. 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 h prior to the assessment to allow an adequate wash-out period; paracetamol could be taken for rescue pain-relief up to 12 h 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 WOMAC was also used to evaluate knee stiffness and function[25].

Pain was assessed using three measures, a visual analogue scale (VAS) from 0 to 100 mm for current KP severity, the pain subscale of the WOMAC questionnaire[25] and the Measure of Intermittent and Constant Osteoarthritis Pain questionnaire (ICOAP)[26].

Standardised, weight-bearing, semi-flexed tibio-femoral and skyline 30° 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)[27,28]. 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)[27]. An overall K/L grade (0–4) was also given to each knee.

US 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[5,29]. 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 <4 mm and present if ≥ 4 mm[5].
(2) Synovial hypertrophy: maximal depth was measured in mm and dichotomised as absent if <4 mm and present if ≥ 4 mm[5].
(3) Baker's cyst: the diameter was measured in the transverse plane and dichotomised as absent if <4 mm or present if ≥ 4 mm[10].
(4) Bursitis: bursae at the infra-patellar tendon and the insertion of the pes-anserinus site were measured and dichotomised as absent if <4 mm or present if ≥ 4 mm infra-patellar bursae, and absent if <2 mm or present if ≥ 2 mm for the pes-anserine bursa[10].
(5) PDS: areas of hypertrophic synovium were scanned. A pulse repetition frequency of 1000–1300 Hz 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)[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 (95% CI, 0.61–0.90). 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