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The responsiveness of novel, dynamic, contrast-enhanced magnetic resonance measures of total knee synovitis after intra-articular corticosteroid for painful osteoarthritis

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SUMMARY

Objective: Sensitive biomarkers are needed to understand synovial response to therapy in osteoarthritis (OA). Dynamic, contrast-enhanced magnetic resonance imaging (DCE MRI) provides quantitative, novel measures of synovial inflammation. This exploratory study examined DCE-assessed synovial response to intra-articular corticosteroid (IACS).

Methods: People with ACR clinical criteria OA knee underwent 3 T MRI pre- and 2 weeks post-IACS. Five MRI variables were assessed blindly: total synovial volume (semi-automated computer program), early enhancement rate (EER) and late enhancement ratio of the entire knee, synovial volume × late enhancement and a semi-quantitative (SQ) score (six sites scored 0–3). Clinical symptoms were assessed using pain visual analogue score (VAS) and WOMAC.

Results: 13 participants (5 male, mean age 63, mean pain VAS 66 mm mean body mass index (BMI) 31.3 kg/m^2) were included. The majority of MRIs demonstrated no change in SQ score although the DCE variables changed to some extent in all. There was generally a reduction in synovial volume ((Wilcoxon test) median (interquartile range (IQR)) reduction 14 cm^3 (−1, 29)), EER (0.2% (−0.3, 0.6)) and late enhancement ratio (8% (−0.5, 41)). Synovial volume × late enhancement ratio demonstrated a substantive reduction (2250 (−930, 5630)) as well as the largest effect size, $r = 0.45$. There was a median 26% reduction in EER in participants with good symptomatic response to IACS, contrasting with a 23% increase in those who responded poorly.

Conclusions: DCE MRI may be more sensitive than a SQ score at detecting post-therapy synovial changes. The association between EER and symptomatic response to IACS may reflect a closer relation of this biomarker to synovial inflammation than with volumetric assessment.

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Introduction

Synovitis is common in osteoarthritis (OA) and large cohort studies using magnetic resonance imaging (MRI) have demonstrated the association between synovitis and pain in OA[1,2]. Anti-inflammatory therapies such as intra-articular corticosteroids (IACS) are an effective treatment for OA pain. Few studies, mostly using ultrasound (US)[3–5], have objectively assessed the synovial response to anti-synovial therapies and changes seen in synovial inflammatory parameters are generally small, and often not associated with clinical symptoms at the patient level.

MRI can perform synovial volumetric analysis, either by manual segmentation or semi-automated methods using specific computer software that may be time-consuming but are currently the gold standard for synovial volume measurement. Semi-quantitative (SQ) synovitis scores are more commonly used which are quicker to perform and have been validated against volumetric analysis[6].

Longitudinal, non-contrast MRI studies have demonstrated an association between an increase in both synovitis and pain[2]; yet a similar reduction in synovitis did not associate with reduced pain[2]. Whilst the lack of structure-pain relationship may reflect the

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complex nature of OA pain and the long time courses between repeat imaging, it may also reflect a relative lack of sensitivity of current MRI scoring systems assessing only synovitis volume.

Dynamic, contrast-enhanced MRI (DCE MRI) measures the rate of enhancement of synovium by intravenous contrast within the synovium and offers an alternative measurement of synovial inflammation. Previous small DCE MRI studies, predominantly of inflammatory arthritis, have demonstrated a reduction in both synovial volume and synovial enhancement rate after IACS[7,8] and DCE MRI has also been used in rheumatoid arthritis[9] and psoriatic arthritis.[10]

This study explored whether a range of DCE MRI parameters assessing all enhancing synovium within an OA knee could demonstrate a change in synovitis after IACS treatment over and above the currently used MR measures of synovitis, thus improving understanding of the association between synovitis and clinical symptoms as well as providing a novel outcome for clinical trials.

Methods

Ethical committee approval was obtained and participants gave written, informed consent. People fulfilling American College of Rheumatology clinical criteria for knee OA, referred from rheumatology secondary care out-patient clinics for IACS due to moderate to severe knee pain, underwent 3 T MRI imaging prior to, and approximately 2 weeks after IACS. Exclusion criteria included inflammatory arthritis, IACS within 8 weeks and recent knee trauma. After the baseline scan, the knee was injected with 80 mg methylprednisolone. Participants at baseline and follow-up completed the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC), and 48 h visual analogue score (VAS) scores for knee pain, patient and physician disease activity. Symptomatic response to IACS was defined by at least a 20% reduction in 48 h pain VAS at the follow-up visit.

Knee radiographs were scored (Kellgren–Lawrence (K/L) method) by a musculoskeletal radiologist (AJG) (intra-reader reliability kappa 0.9).

Images were acquired using a 3T Magnetom Verio scanner (Siemens, Erlangen, Germany) using a standard eight channel knee coil or a larger 15 channel coil. 30 3D gradient echo images were acquired before, during and after administration of ~0.1 mmol/kg (max dose 10 mmol) Dotarem (Guerbet, France) at 4 ml/s (TR = 4.3 ms, TE = 2.5 ms, flip-angle = 30°, matrix size 256 × 90, field of view 300 × 131/330 × 144 mm, slice thickness 1.3 mm, GRAPPA with IPAT = 3, acquisition time 10 s). High resolution VIBE images (TR = 8 ms, TE = 2.9 ms, flip-angle = 30°) were acquired after contrast administration. Synovitis was scored by a musculoskeletal radiologist (AJG) blinded to patient data and time order, using an SQ score (maximum 14) assessing six areas: medial and lateral parapatellar recesses, suprapatellar pouch, infrapatellar fat pad (0–3), and the medial and lateral condyles (0–1).[6]

Total synovial volume was calculated using the Analyze software (version 10.0). Difference images were created from the first pre-gadolinium series and the final post-gadolinium series.

Semi-automatic segmentation of the enhancing synovium was performed from the difference images of the entire knee joint using a combination of thresholding functions and manual correction. The 3D segmentation was overlaid on the 4D dynamic series and values for total synovial volume and mean synovial signal intensity (SI) for each dynamic series generated. The mean early enhancement rate (EER) at 60 s was calculated by the formula: $\{[SI_{t60} - SI_{t0}]/[SI_{t0} \times 60]\} \times 100\%$, and the late enhancement ratio by: $\{[SI_{t250} - SI_{t0}]/SI_{t0}\} \times 100\%$, where SI represents the mean synovial enhancement at a time point (t).

The "total synovial enhancement", was calculated by multiplying the total synovial volume by the late enhancement ratio.

Statistical analysis

This was an exploratory study and was not powered to show statistical significance. Statistical analysis was performed using IBM SPSS v.20 (IBM, USA). Wilcoxon signed rank test compared the difference in variables before and after IACS, and Spearman's rank order correlation test assessed correlation between variables. Effect sizes for the Wilcoxon signed rank (r) were calculated as the z-statistic divided by the square root of the total number of observations[11].

The standardised response mean (SRM) assessed sensitivity to change for each MR variable in this homogenous group of participants. The modified Jackknife technique tested whether the differences in SRM values between the synovial volumetric analysis (seen as the gold standard) and the early, late and total synovial enhancement were significant[12]. A linear regression model predicts the difference between the SRM of the gold standard variable and that of a comparative variable. The model intercept coefficient represents the difference between the SRM of the gold standard and that of the comparative variable − a negative value the intercept coefficient indicates that the SRM for that variable is lower that the SRM of the gold standard.

Results

20 participants were recruited (mean age 63 years, mean 48 h pain VAS 73 mm). Data from seven participants were later excluded due to difficulty establishing intravenous access ($n = 3$), hardware failure ($n = 3$); subject movement ($n = 1$). Participant demographics are reported in Table I.

All 13 participants had synovitis at baseline, as defined by a baseline SQ score of >1 (median score 8), (intra-reader reliability kappa 0.85). As previously reported, the SQ score demonstrated a marked correlation with total synovial volumetric analysis (rho 0.66, 95% C.I. 0.10–0.87). Five demonstrated a change in SQ score after IACS, but in the majority the score remained unchanged (median 0; effect size $r = 0.36$). In contrast, DCE MRI demonstrated a change at the individual participant level in synovial volume and in early, late and total synovial enhancement in all participants, even in the absence of a change in SQ score (Fig. 1). At the group level the effect sizes after IACS were generally small for all DCE variables, but the novel variable, total synovial enhancement demonstrated a larger effect size ($r = 0.45$), than for changes in early ($r = 0.18$) and late enhancement ($r = 0.32$) and total synovial volume ($r = 0.33$) and SQ synovitis score ($r = 0.36$) (Table I).

A moderate association was suggested between the late enhancement ratio and both WOMAC pain score (rho 0.49, 95% CI −0.11 to 0.9) and 48 h pain VAS (rho 0.41, −0.21 to 0.83), but the confidence intervals were broad and non-statistically significant from zero. There were no associations between change in clinical variables and change in MR variables (all rho <0.2 or $P > 0.05$).

Participants who achieved a good symptomatic response to IACS had a median 26% reduction (interquartile range (IQR) 6%, 45%) in EER contrasting with a 19% (IQR −32%, 79%) increase in EER in those who had poor response (effect size $r = 0.34$, $P = 0.086$). There were similar differences in the changes in late static enhancement (good response, median reduction (IQR) 29% (7%, 39%) vs poor response, median reduction (IQR) 1% (−42%, 37%); $r = 0.25$; $P = 0.199$).

The novel variable of total synovial enhancement had the highest SRM value (0.73) compared with the gold standard of synovial volumetric analysis (0.45). The EER and late enhancement

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