Degree of synovitis on MRI by comprehensive whole knee semi-quantitative scoring method correlates with histologic and macroscopic features of synovial tissue inflammation in knee osteoarthritis

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**SUMMARY**

Objective: To evaluate the association between synovitis on contrast enhanced (CE) MRI with microscopic and macroscopic features of synovial tissue inflammation.

Method: Forty-one patients (mean age 60 years, 61% women) with symptomatic radiographic knee OA were studied: twenty underwent arthroscopy (macroscopic features were scored (0 e 4), synovial biopsies obtained), twenty-one underwent arthroplasty (synovial tissues were collected). After haematoxylin and eosin staining, the lining cell layer, synovial stroma and inflammatory infiltrate of synovial tissues were scored (0 e 3). T1-weighted CE-MRI’s (3 T) were used to semi-quantitatively score synovitis at 11 sites (0 e 22) according to Guermazi et al. Spearman’s rank correlations were calculated.

Results: The mean (SD) MRI synovitis score was 8.0 (3.7) and the total histology grade was 2.5 (1.6). Median (range) scores of macroscopic features were 2 (1 e 3) for neovascularization, 1 (0 e 3) for hyperplasia, 2 (0 e 4) for villi and 2 (0 e 3) for fibrin deposits. The MRI synovitis score was significantly correlated with total histology grade \([r = 0.6]\), as well as with lining cell layer \([r = 0.4]\), stroma \([r = 0.3]\) and inflammatory infiltrate \([r = 0.5]\) grades. Moreover, MRI synovitis score was also significantly correlated with macroscopic neovascularization \([r = 0.6]\), hyperplasia \([r = 0.6]\) and villi \([r = 0.6]\), but not with fibrin \([r = 0.3]\).

Conclusion: Synovitis severity on CE-MRI assessed by a new whole knee scoring system by Guermazi et al. is a valid, non-invasive method to determine synovitis as it is significantly correlated with both macroscopic and microscopic features of synovitis in knee OA patients.

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Introduction

For a long time, OA was considered a non-inflammatory condi-
tion. More recently, however, it became evident that synovial
inflammation could play an important role in the pathophysiology
of OA as it is a predictor of cartilage destruction and a deter-
minant of pain. Although the biological processes underlying
the appearance of synovial inflammation are poorly understood, it has
been suggested that cartilage breakdown products could lead to
activation of immune cells and production of pro- and anti-
flammatory mediators, which in turn could stimulate further
cartilage breakdown, creating a negative feedback loop in OA.
Likewise, it is unclear how synovial inflammation evolves during
the disease course, since studies investigating this topic were
conflicting. Therefore, more studies are necessary to elucidate
the evolution of synovial inflammation during the disease course.

Histological assessment of synovial biopsies is currently the
standard for evaluating synovitis in knee OA. However, acquisi-
tion of synovial biopsies is technically difficult and patient
unfriendly as it involves an invasive procedure like arthroscopy.

In the present study, we aimed at validating the assessment of
synovitis on CE-MRI with histology samples. Synthetic assess-
ment has been approved by the ethics committee of the Leiden
University Medical Center (LUMC). All patients provided written
consent. The geMstoan study comprises of two groups of patients: one group of patients with end-stage disease that were planned to receive an arthroplasty and another group with mild to established OA that had no indication for an arthroplasty. Patients with mild to established disease received an arthroscopy.

Patients with other rheumatic diseases, using immunosup-
pressive drugs or having knee injections (corticosteroids, etc) in the
past 3 months were excluded. Patients with renal insuf-
ciency (Cockcroft-Gault < 60 mL/min) did not undergo CE-MRI. Patients
using anti-coagulants did not undergo arthroscopy. Patients having
both synovial tissue samples and CE-MRI images were included in
the present study.

Arthroscopy and macroscopic scoring of synovial tissue

Arthroscopy was performed only for the purpose of this
research study, using a small-bore 2.7 mm arthroscope (Storz,
Turrlingen, Germany) with sterile technique, as described previ-
ously. After maximal needle aspiration of synovial fluid, intra-
articular and local skin anaesthesia was achieved by a lidocaine
injection (1%). The skin inferolateral to the patella was also injected
with lidocaine 0.5%. Two small skin incisions were made to intro-
duce two portals into the joint. The lower portal was used for intro-
duction of the arthroscope and instillation of saline. The upper
portal was used for collecting 15–20 blind synovial tissue biopsies
and draining of the saline. Biopsies were taken from the patellar
regions of the medial capsule using 2.0 mm forceps. All biopsies
were physically combined to create one tissue block. Arthroscopic
exploration was combined with joint lavage with at least 1000 ml of
saline. At the end of the procedure 6 ml of 0.5% marcaine was
administered.

During the procedure macroscopic features (neovascularization,
villi, fibrin deposits and hyperplasia) were visualized by using a 30°
flex scope (magnification 40 ×) and the general appearance of sy-
novial tissue was semi-quantitatively scored from 0 to 4 (0 = ab-
sent, 1 = little, 2 = moderate, 3 = much/many, 4 = very much
present/very many) by one physician according to a non-validated
scoring method, which has been used for over 10 years in our
centre. The physician was blinded for imaging data during
evaluation.

Methods

Study design

This study is part of the ongoing GEneration of Models, Mech-
anism & Markers for STratification of OsteoArthritis patieNts study
(geMstoan), an observational study in established and end-stage
knee OA patients to find new biomarkers for OA progression. This
study has been approved by the ethics committee of the Leiden
University Medical Center (LUMC). All patients provided written
consent.

Patients

Between 2008 and 2012, patients with symptomatic radi-
ographic primary knee OA, following the clinical and radiographic
ACR criteria set, attending the rheumatology or orthopaedic
department of the LUMC or orthopaedic department of the
Diaconessenhuis, Leiden, were included. The geMstoan study
comprises of two groups of patients: one group of patients with
end-stage disease that were planned to receive an arthroplasty and
another group with mild to established OA that had no indication
for an arthroplasty. Patients with mild to established disease received an arthroscopy.

Synovial tissue samples were collected from patients admitted
for arthroplasty for OA to the orthopaedic departments. One sample of 3 × 3 × 3 mm was obtained from a random location form the
knee.

Scoring synovial tissue samples handling and staining

All synovial tissue samples were fixated in formalin for
approximately 24 h and then transferred to 70% ethanol in which
they were stored until they were imbedded in paraffin. Fifty-
five μm thick coupons were cut. From 50 coupons of tissue, three
coupons in the beginning of the tissue block and three coupons from
the middle part of tissue block were selected and stained
with haematoxylin and eosin (H&E) after deparaffinization. From these
2–6 coupons for each patient had a high enough quality to be scored.
modified in the present study as follows: for each feature the samples with the least severe and the most severe score were determined and they provided the basis for developing a scoring system for each feature ranging from 0 (least severe) to 3 (most severe) (Fig. 1). Subsequently, all synovial tissue samples were scored by three independent observers who were blinded to MRI and clinical data; for each feature an average grade was calculated (0–3) for each patient. Furthermore, a total grade was calculated (sum of averaged grades of all three features (0–9)). In case the scoring of one observer was evidently different from the other two, one rescoring was performed by that observer.

MRI acquisition

Patients underwent MRI of the index knee less than 7 days and more than 36 h before the arthroscopy. MR scanning was performed on a 3 T MR system (Philips Achieva, Philips Healthcare, Best, The Netherlands) using an eight-channel dedicated knee coil. Gadolinium (Gd) contrast agent (Gd-DOTA, Dotarem, Guerbet, 0.2 ml/kg @ 2 ml/s followed by a saline flush 40 ml @ 2 ml/s) was injected in the cubital vein for visualizing synovitis. Both axial and sagittal CE, T1-weighted, turbo spin echo (TSE), spectral presaturation with inversion recovery (SPIR) sequences were used for the analysis (range 0–22). A total score of 0–4 was considered normal (no synovitis); 5–8 represents a mild, 9–12 a moderate and above 13 a severe synovitis. All MR images were analysed by means of consensus between two readers both experienced in reading MR images of the knee (BDL and WV). Both BDL and WV (over 1000 MRI's scored) have more than 3 years of experience in scoring knee MR images. Scoring was done after extensive learning sessions and under supervision of experienced musculoskeletal radiologist (JB).

During the assessment, the readers were blinded to radiographic results and patient data. Intraclass correlation (ICC, with 95% confidence interval (CI)) was based on random sample of 14 CE-MRI's and was 0.84 (0.58–0.95).

MRI scoring

Sagittal and axial T1-weighted CE-MR images (3 T) were used to semi-quantitatively score synovitis at 11 different sites according to Guermazi et al. Ref. 16. Synovial thickness was measured and scored as followed: 0, when synovial thickness was less than 2 mm, 1 when thickness was between 2 and 4 mm and 2 when synovial thickness was above 4 mm. The total sum score of 11 sites was used for the analysis (range 0–22). A total score of 0–4 was considered normal (no synovitis); 5–8 represents a mild, 9–12 a moderate and above 13 a severe synovitis. All MR images were analysed by means of consensus between two readers both experienced in reading MR images of the knee (BDL and WV). Both BDL and WV (over 1000 MRI’s scored) have more than 3 years of experience in scoring knee MR images. Scoring was done after extensive learning sessions and under supervision of experienced musculoskeletal radiologist (JB).

During the assessment, the readers were blinded to radiographic results and patient data. Intraclass correlation (ICC, with 95% confidence interval (CI)) was based on random sample of 14 CE-MRI’s and was 0.84 (0.58–0.95).

Scoring knee radiographs

Radiographs (posterior anterior (PA) fixed flexion) were obtained for all patients.

Radiographs were scored, blinded for patient characteristics, by an experienced musculoskeletal radiologist (HK), with 30 years of experience in scoring musculoskeletal radiographs, according to the Kellgren–Lawrence (KL) scale23. The ICC, with 95% CI was based on a randomly selected sample of 36 radiographs (17 right and 17 left knees) and was 0.99 (0.98–0.99). The knees with KL < 2 were rescoring in consensus between HK and an experienced rheumatologist reader (MK).

Clinical data

Self-reported pain of the index knee was assessed by the visual analogue scale (VAS, 0–100) within 2 weeks of MRI acquisition.

Statistics

Parameters normally distributed are described as means (SD), otherwise medians (ranges) are given. Comparison between groups was calculated with independent t-test for MRI synovitis score, total histology grade, age, fat percentage and VAS, and Mann–Whitney U test for histology features, KL grade and BMI. Chi-squared test was used for comparison of proportions for gender and index knee, Chi-squared test for trend was used for comparison of BMI groups, KL grade groups and MRI synovitis groups. Spearman’s rank correlations for all patients were used for correlation between total MRI synovitis score and total histology synovitis grade, histology features, macroscopy features and VAS. A correlation < 0.3 was considered as weak, 0.3–0.7 as moderate and >0.7 as strong. SPSS 20.0 was used for statistical analyses.

Results

Patient characteristics

Of 95 patients included in the geMstoan study, 42 patients had both CE-MRI and synovial tissue available. Those 42 patients did not differ for age, sex, BMI, fat percentage, KL grade or VAS pain from original 95 patient samples (data not shown). One patient developed after 1 year a CCP positive, rheumatoid factor positive...
Histology of synovial tissue of OA patients (Table III) showed less synovial thickness at all sites. The arthroscopy group had a mean (SD) synovitis score on MRI for all patients was 8.0 (3.6) higher in the arthroplasty group (9.7 (3.8)). The mean (SD) synovitis score on MRI for all patients was 8.0 (3.6) for the arthroscopy group vs 1 (0.2) for the arthroplasty group. For the infiltrate median (range) was 0.2 (0–3). For the stroma and 0.5 for the infiltrate. Overall, 60% of patients showed an inflammatory infiltrate. More patients in the arthroplasty group showed infiltrates (69%) compared to the arthroscopy group (50%).

The mean (SD) total histology grade differed significantly between patients with mild/established and patients with end-stage knee OA (2.0 (1.4) vs 3.0 (1.7), respectively). The grades for both the lining layer and inflammatory infiltrate were significantly higher in the arthroplasty group. Median (range) for the lining layer was 0.5 (0–2.8) for the arthroscopy group vs 1 (0–2.5) for the arthroplasty group. The grade infiltrate (range) was 0.2 (0–1.8) vs 0.9 (0–3). For the stroma no significant differences were seen between the groups. Representative examples of histology features of a patient in both groups are displayed in Fig. 2.

Macroscopy features assessed during arthroscopy

In 22 patients undergoing arthroscopy, the median (range) score for macroscopic features was 2 (1–3) for neovascularization, 1 (0–3) for hyperplasia, 2 (0–4) for villi and 2 (0–3) for fibrin.

Correlations between synovitis assessed by CE-MRI, histology and macroscopy and association with pain

As summarized in Table IV, there was a moderate significant correlation between the total synovitis grade on MRI and the total histology grade, lining layer, stroma cells and inflammatory infiltrate. Furthermore, the MRI synovitis grade was significantly correlated with the macroscopic features: neovascularization, hyperplasia and villi, but not with fibrin. A significant correlation between total histology grade and the macroscopic neovascularization was seen as well. Moreover, a moderate, but statistically significant correlation was seen between the MRI synovitis score and the VAS pain level. In

<table>
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<tr>
<th>Parameters</th>
<th>All</th>
<th>Arthroscopy group</th>
<th>Arthroplasty group</th>
<th>Diff (95% CI)/P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, mean (SD)</td>
<td>60.2 (9.0)</td>
<td>60.8 (7.2)</td>
<td>59.7 (10.7)</td>
<td>1.0 (–4.7 to 6.8)*</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>25 (61.0)</td>
<td>14 (70.0)</td>
<td>11 (52.4)</td>
<td>P = 0.248***</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Total, median (range)</td>
<td>29.1 (22.2–43.9)</td>
<td>29.2 (24.4–43.9)</td>
<td>29.1 (22.2–40.9)</td>
<td>P = 0.696**</td>
</tr>
<tr>
<td>- Groups, no. (%)</td>
<td>-</td>
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<tr>
<td>- &lt;25</td>
<td>4 (9.8)</td>
<td>1 (5.0)</td>
<td>3 (14.3)</td>
<td>P = 0.704****</td>
</tr>
<tr>
<td>- 25–30</td>
<td>23 (56.1)</td>
<td>13 (65.0)</td>
<td>10 (47.6)</td>
<td>-</td>
</tr>
<tr>
<td>- 30–35</td>
<td>9 (22.0)</td>
<td>3 (15.0)</td>
<td>6 (28.6)</td>
<td>-</td>
</tr>
<tr>
<td>- 35–40</td>
<td>2 (4.9)</td>
<td>1 (5.0)</td>
<td>1 (4.8)</td>
<td>-</td>
</tr>
<tr>
<td>- &gt;40</td>
<td>3 (7.3)</td>
<td>2 (10.0)</td>
<td>1 (4.8)</td>
<td>-</td>
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<tr>
<td>Fat percentage, mean (SD)</td>
<td>36.6 (8.4)</td>
<td>38.5 (8.1)</td>
<td>34.8 (8.4)</td>
<td>3.7 (–1.5 to 9.0)*</td>
</tr>
<tr>
<td>Right knee, no. (%)</td>
<td>25 (61.0)</td>
<td>11 (55.0)</td>
<td>14 (66.7)</td>
<td>P = 0.444***</td>
</tr>
<tr>
<td>KL grade</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Total, median (range)</td>
<td>3.0 (1–4)</td>
<td>2.0 (1–4)</td>
<td>3.0 (2–4)</td>
<td>P &lt; 0.001**</td>
</tr>
<tr>
<td>- Groups, no. (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- 1</td>
<td>2 (4.9%)</td>
<td>2 (10.0%)</td>
<td>0</td>
<td>P &lt; 0.001****</td>
</tr>
<tr>
<td>- 2</td>
<td>12 (29.3%)</td>
<td>11 (55.0%)</td>
<td>1 (4.8%)</td>
<td>-</td>
</tr>
<tr>
<td>- 3</td>
<td>16 (39.0%)</td>
<td>6 (30.0%)</td>
<td>10 (47.6%)</td>
<td>-</td>
</tr>
<tr>
<td>- 4</td>
<td>11 (26.8%)</td>
<td>1 (5.0%)</td>
<td>10 (47.6%)</td>
<td>-</td>
</tr>
<tr>
<td>VAS pain knee, mm, mean (SD)</td>
<td>52.4 (21.4)</td>
<td>42.9 (23.6)</td>
<td>61.4 (14.5)</td>
<td>–18.5 (–31.0 to –5.9)*</td>
</tr>
</tbody>
</table>

Table I

Patients characteristics of all (n = 41) patients and different groups: patients receiving arthroscopy (n = 20) and patients receiving arthroplasty (n = 21).

* Independent t-test, ** Mann–Whitney U test, ***Chi-squared test and **** Chi-squared trend test.

Table II

MRI synovitis total scores and distribution of severity of synovitis score at MRI in patients with knee OA

* Independent t-test, **** Chi-squared trend test.

Synovitis on CE-MR images (Table II)

The mean (SD) synovitis score on MRI for all patients was 8.0 (3.7), representing a mild synovitis, and was significantly lower in patients in the arthroscopy (6.1 (2.6)) than in the arthroplasty group (9.7 (3.8)); mean difference –3.6 (95% CI –5.7 to –1.6). Representative examples of CE-MR images of patient from both groups are displayed in Fig. 2.

When all 11 sites on CE-MRI were investigated and compared between the arthroscopy and the arthroplasty group, no patients in the arthroscopy group had a total MRI score representing a severe synovitis, whereas five patients (24%) in the arthroplasty group had. Overall, the arthroplasty group showed increased synovial thickness at all 11 different sites, while the arthroscopy group showed less synovial thickness at all sites.

Histology of synovial tissue of OA patients (Table III)

A mean total histology grade of 2.5 was observed for all patients. Medians in all patients were 0.8 for the lining layer, 0.9 for the stroma and 0.5 for the infiltrate. Overall, 60% of patients showed an inflammatory infiltrate. More patients in the arthroplasty group showed infiltrates (69%) compared to the arthroscopy group (50%).
arthroscopy group correlation of MRI synovitis score with total histology grade was a little bit higher 0.58 ($P = 0.007$), while in the arthroplasty groups the correlation was lower 0.45 ($P = 0.041$).

**Discussion**

To our knowledge we are the first to validate a new comprehensive and practical synovitis scoring method for assessing degree of synovitis on CE-MRI in the whole knee. We found a significant correlation of total synovitis score on MRI with both macroscopic and microscopic features of synovitis, which indicates that the method by Guermazi et al.\textsuperscript{16} is a valid method to assess degree of inflammation in knee OA patients. A significant correlation between VAS pain scores and synovial inflammation on CE-MRI was also seen. Furthermore we found that the total histology grade and the MRI synovitis score was less in patients undergoing an...
arthroscopy, representing a mild to established knee OA patient group, than in patients receiving an arthroplasty, representing end-stage knee OA. Therefore, it seems that synovial inflammation is a more pronounced feature of end-stage knee OA patients.

In the present study we found a moderate significant correlation of synovitis severity on MR images with both histological and macroscopic features of synovitis and with pain scores. Our correlation with pain was as expected moderate (0.3), while pain is multidimensional and other dimensions of pain (depression, personality, etc.) were not included in our study. Our dedicated set-up enabled us to find these correlations. Firstly, synovial inflammation was scored on contrast enhanced (CE) MR images, as this is the best way to distinguish synovial inflammation from synovial fluid and fat tissues. Studies that investigated the correlation cross-sectionally between severity of only synovitis (not the combination of synovitis and effusion) in osteoarthritis assessed on non-CE MR images and VAS pain, no significant correlation was found. Secondly, we used a 3 T scanner, instead of a 1.5 T scanner, which is more often used, but have a lower signal to noise ratio. Finally, in the present study extensive synovitis scoring was performed addressing 11 sites in the whole knee. These advantages may explain the differences with other studies performed in the same research field. Loeuille et al. assessed synovitis on MR images and performed a validation with clinical symptoms, histology samples and macroscopic features. Although contrast enhancement was used, no correlation was found between the MRI synovitis score and VAS pain. Furthermore, a lower correlation with histology was found (r = 0.41 vs 0.6 in the present study). The lower correlations found could be explained by the use of a scoring method for synovitis severity on MR images addressing only five sites in the knee. The present extensive scoring would have allowed more comprehensive evaluation.

The aim of present study was to investigate whether synovitis on CE-MR as assessed in all compartments of the knee could be used as surrogate for synovial tissue inflammation. Therefore, we compared total MRI score with the total histology grade. In arthroplasty patients we investigated a random sample of synovial tissue from the knee, while in the arthroscopy group we evaluated the medial capsule, since this is the only site that can be reached safely. It could have been possible that the correlation of the total score on MRI with the total histology score would have been higher in arthroscopy patients if we had biopsies from the whole knee instead of only at a selected site of all our patients or if we had performed visualized sampling of the tissue to assess the exact location of the biopsies enabling more direct comparisons. However, this was not observed since the correlation between the MRI score of the two medial sites (creating a range 0–4) with the total histology grade in the arthroscopy patient group (n = 20), was the same (0.58 (P = 0.008)) as the correlation between the total MRI score and total histology grade in the arthroscopy group (0.58 (P = 0.007)). This observation suggests that sampling of the medial site during arthroscopy is a good representation of the synovitis in the whole knee, but these results should be interpreted with caution.

New in this study is the extensive investigation of synovitis in different stages of OA. Not only were both MRI and histology used to compare mild to established OA to end-stage disease, but we were also able to study real mild to established knee OA since we investigated patients with knee OA without a clinical indication for arthroscopy. MRI and histology data, although scored independently of each other, are supporting each other. We found that the patients with end-stage OA, had a higher MRI synovitis score, a higher total histology score of the synovial biopsies and reported more pain, compared to patients with mild to established OA. In the literature results regarding the degree of synovial inflammation at different stages of OA are conflicting and vary from no difference to more inflammation in patient with earlier than in end-stage OA or to more inflammation in patients with end-stage than in earlier OA. Differences in results between the studies could be explained by dissimilarity in defining the stage of OA in the cases under study, and by the methods used to score the histological samples and MR images. In a study by Pearle et al. in primary OA patients no differences were found in the prevalence of synovial infiltrates between early and advanced OA. Early OA was defined as KL grade ≤ 2 and no intraoperative evidence of full-thickness chondral wear, while advanced was defined as KL > 2 and intraoperative evidence of full-thickness chondral loss. In this study no MR imaging was performed and the sample size of the patients in the early group was only 9, vs 43 in the advanced group Pearle et al. In a study by Benito et al. more pronounced inflammation was seen in early OA patient group than in end-stage OA. Early OA was defined when patients had clinical features of OA and cartilage degeneration during arthroscopy, but no radiographic OA signs, which is different from the present study where all patients had radiographic knee OA. In the study by Benito et al. also no MR images were available. Two studies found a higher synovitis severity score in late-stage OA than in earlier phases of the disease as in the present study. Loeuille et al. found microscopically a significantly lower mean total composite score and infiltration score for the early OA (mild cartilage lesions at arthroscopy) group than for the end-stage (severe cartilage lesions with exposure of subchondral bone at arthroscopy) group, but no difference in MRI synovitis score between the groups. Smith et al. found in a

<table>
<thead>
<tr>
<th>Table III</th>
<th>Histological total synovitis grade and distribution of histological features in patients with knee OA</th>
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</thead>
<tbody>
<tr>
<td>Histological synovitis grade</td>
<td>All patients (n = 41)</td>
</tr>
<tr>
<td>Total (0–9), mean (SD)</td>
<td>2.5 (1.6)</td>
</tr>
<tr>
<td>Features, median (range)</td>
<td></td>
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<tr>
<td>Lining layer (0–3)</td>
<td>0.8 (0–2.8)</td>
</tr>
<tr>
<td>Stroma (0–3)</td>
<td>0.9 (0–2.7)</td>
</tr>
<tr>
<td>Infiltrate (0–3)</td>
<td>0.5 (0–3)</td>
</tr>
</tbody>
</table>

*A independent t-test, ** Mann–Whitney U test.

<table>
<thead>
<tr>
<th>Table IV</th>
<th>Correlations between macroscopic features at arthroscopy, histological synovitis grade and pain score with total MRI synovitis score in patients with knee OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters</td>
<td>Spearman’s rank correlations</td>
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<td>Macroscopy (n = 20)</td>
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<tr>
<td>Neovascularization (0–4)</td>
<td>0.64</td>
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<tr>
<td>Hyperplasia (0–4)</td>
<td>0.64</td>
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<tr>
<td>Villi (0–4)</td>
<td>0.61</td>
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<tr>
<td>Fibrin (0–4)</td>
<td>0.34</td>
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<tr>
<td>Histology (n = 41)</td>
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<tr>
<td>Total synovitis grade (0–9)</td>
<td>0.57</td>
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<tr>
<td>Lining layer (0–3)</td>
<td>0.38</td>
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<td>Stroma (0–3)</td>
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<td>Infiltrate (0–3)</td>
<td>0.47</td>
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<td>VAS pain (n = 41)</td>
<td>0.32</td>
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histological study more infiltrate and a trend towards increased synovial lining layer in end-stage OA, when compared to early OA\textsuperscript{11}.

The present study has some limitations. A relatively small number of patients were included in the present study (n = 41), therefore findings should be interpreted with caution and should be replicated in larger samples.

Furthermore, in the present study we scored macroscopic features according to a non-validated method. Moreover, reproducibility could not be done, because repetitive procedures are not ethical. However the person performing the arthroscopy was blinded for CE-MRI data, therefore misclassification is random. But, taken together data concerning macroscopic features should be interpreted with caution.

The time from Gd injection to acquisition of T1-W images was 8–10 min due to the fact that our protocol included several dynamic sequences (that are not part of the current analysis). Although, some controversy exists concerning the optimal time after Gd injection\textsuperscript{17,18,20}, we feel this could have potentially have led to washout of the contrast into the cavity and might have led to increased measurements of synovial thickness. However, because the aim of present study was to compare findings between patients and in all patients the time after injection was comparable, the actual measurements of synovial membrane were of lesser importance and this is less of a problem.

Finally, we modified the validated histological synovitis scoring system by Krenn \textit{et al.} Therefore our mean total histology scores cannot be compared to results that use the synovitis score by Krenn \textit{et al.} Ref.\textsuperscript{22}. However this modification made our score more sensitive to discriminate between groups.

In present study we validated a new whole knee scoring system on CE-MRI by Guermazi \textit{et al.} by comparing synovial inflammation on CE-MRI with histological and macroscopic features of the synovial tissue. Furthermore, we have shown that synovial inflammation was more prevalent and severe in end-stage knee OA and that synovial inflammation is of clinical importance as it is associated with pain. Further research is necessary to elucidate the role of synovitis in the pathophysiology in OA.

\textbf{Author contributions}

Authors made substantial contributions to the following: (1a) conception and design of the study: BDL, GVO, AMZ, VSS, TH, MK; (1b) acquisition of data: BDL, AIF, EY, AWV, HK, SA, LVT, JB, RN, MK; (1c) interpretation of data BDL, AIF, GVO, AMZ, VSS, JB, TH, MK; (2) drafting or critical revision of manuscript: BDL, AIF, EY, AWV, HK, SA, LVT, GVO, AMZ, VSS, JB, RN, TH, MK; (3) final approval of manuscript BDL, AIF, EY, AWV, HK, SA, LVT, GVO, AMZ, VSS, JB, RN, TH, MK.

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Financial support was obtained from Ti Pharma, however Ti Pharma did not contribute to design, interpretation of data, drafting and final approval of the manuscript.

\textbf{Conflict of interests}

None.

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\textbf{References}


