Macroscopic and Microscopic Features of Synovial Membrane Inflammation in the Osteoarthritic Knee

Correlating Magnetic Resonance Imaging Findings With Disease Severity

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Objective. **To determine the magnetic resonance imaging (MRI), macroscopic, and microscopic characteristics of synovial membrane inflammation, to study the relationship between disease severity and the degree of synovial inflammation on MRI and on macroscopic and microscopic examination, and to look for colocalization of chondral lesions and synovial inflammation.**

Methods. **Thirty-nine patients with knee osteoarthritis (OA) were classified into 2 groups according to the severity of cartilage lesions as revealed by chondroscopy. Group 1 (n = 14) had mild cartilage lesion(s) without exposure of subchondral bone. Group 2 (n = 25) had severe cartilage lesion(s) with focal or diffuse exposure of subchondral bone. Synovitis was evaluated on T1-weighted MRI sequences according to the degree of synovial thickening on a 4-point scale (ranging from 0 to 3) in 5 regions of interest. Synovial membrane was macroscopically scored, and biopsies were performed on the 5 preselected sites for histologic scoring.**

Results. **The mean ± SD synovial thickening score on MRI was 1.55 ± 0.90, with no significant difference between groups 1 and 2. Intra- and interobserver reproducibility of the total synovial score was excellent, and interobserver reproducibility of the MRI grade was good. Synovitis was diffuse and associated with chondral lesions only in the medial femorotibial compartment (r = 0.49, P = 0.001). The degree of synovial thickening on MRI correlated with qualitative macroscopic analysis (r_s = 0.58, P < 0.001) and with microscopic features (synovial lining cells [r_s = 0.23, P < 0.007], surface fibrin deposition [r_s = 0.12, P < 0.01], fibrosis [r_s = 0.31, P < 0.006], edema [r_s = 0.17, P = 0.07], congestion [r_s = 0.30, P < 0.005], and infiltration [r_s = 0.46, P < 0.0001]). Fibrin and infiltration parameters were more severe in end-stage disease (P = 0.009 and P = 0.02, respectively).**

Conclusion. **Synovitis may be present from the onset of OA and may be evaluated on MRI. MRI evaluation of synovitis could be used to classify OA patients in clinical trials and could help to identify those who could benefit from synovium-targeted therapy.**
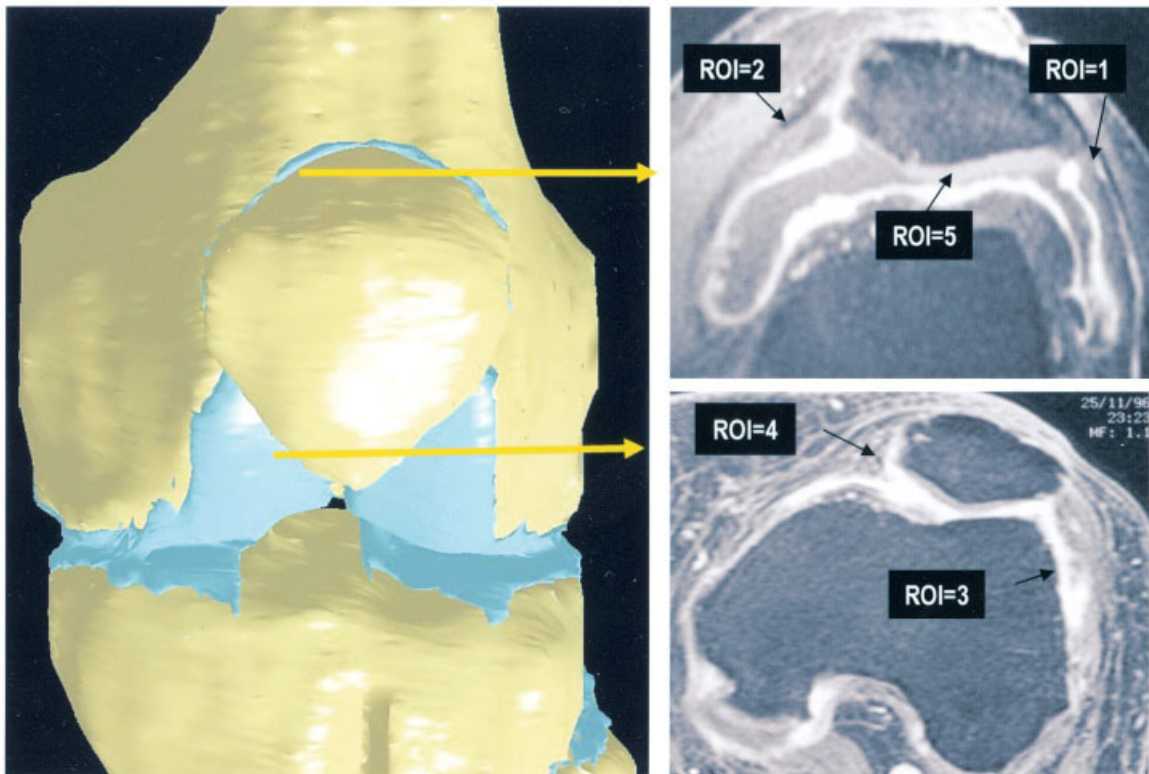
Osteoarthritis (OA) is the most prevalent form of arthritis and a major cause of disability worldwide (1). Structural changes in the OA joint have been difficult to

Figure 1. Magnetic resonance imaging evaluation of synovial membrane inflammation. Synovial membrane inflammation was investigated in 5 regions of interest (ROIs) on axial postinjection T1-weighted sequences. These ROIs included 3 in the suprapatellar recess (lateral recess [ROI 1], medial recess [ROI 2], and just above the trochlear groove [ROI 5]) and 1 each in the lateral and medial femoral gutters (ROIs 3 and 4, respectively). Slices selected for grading of synovial membrane inflammation corresponded to the first and the last axial slices in which the patella was still visible.

study because of our inability to evaluate synovial inflammation coupled with the failure of conventional radiography to depict early cartilage lesions. Synovitis is an important characteristic of chronic inflammatory joint diseases of autoimmune origin, such as rheumatoid arthritis (RA) and spondylarthropathy (SpA) (2–5). It can also occur as a secondary inflammatory symptom in OA, when it is primarily induced by biochemical stress on cartilage.

Most studies in OA have been performed on synovial tissue obtained at the time of surgery, thereby biasing patient selection in terms of disease severity and activity (6). It is unclear whether the observed macroscopic and microscopic changes are of primary pathogenic relevance or secondary bystander phenomena due to chronic joint inflammation and exposure of subchondral bone. The prevalence of synovial abnormalities in patients with early OA is not well studied, but Fernandez-Madrid et al reported that synovial thickening was depicted on T2-weighted sequences in 73% of

joints with early OA (7). Gadopentetate dimeglumine (gadolinium diethylenetriaminepentaacetic acid [Gd-DTPA])–enhanced magnetic resonance imaging (MRI) permits differentiation of inflamed synovium and has been proposed as a potentially valuable tool in evaluating synovitis, particularly in RA and SpA (8–10). However, it has yet to be reported as a means of precisely evaluating synovial membrane inflammation in different stages of OA. Moreover, most microscopic evaluations of the synovial membrane have been performed on synovial samples obtained from patients with end-stage disease.

Against that background, the objectives of the present study were as follows: 1) to determine the MRI, macroscopic, and microscopic characteristics of synovial membrane inflammation in patients with various stages of knee OA; 2) to study the relationship between disease severity (as determined by arthroscopic examination [the gold standard]) and the degree of synovial inflammation on MRI and on macroscopic and microscopic

examination; and 3) to investigate for colocalization of chondral lesions and synovial inflammation.

PATIENTS AND METHODS

Patients. The 39 enrolled patients (18 men and 21 women) fulfilled the American College of Rheumatology criteria for knee OA (11) and required joint lavage due to the presence of chronic joint effusion and the absence of response to corticosteroid injection or general treatment. Patients with evidence of crystal-induced disease, traumatic injury, or active inflammatory disorder were excluded.

Assessment. Demographic data and other characteristics were recorded at baseline. Function and pain were evaluated using Lequesne's index (12) and a visual analog scale (VAS), respectively. Standard blood tests were conducted, including those for C-reactive protein (CRP) serum level (Hitachi 911; Roche Diagnostics, Mannheim, Germany) and erythrocyte sedimentation rate (ESR). Clinical examination to detect joint effusion was performed just before arthroscopy. Radiographic evaluation consisted of bilateral anteroposterior weight-bearing knee radiographs with the knee fully extended. The most affected femorotibial compartment and the femoropatellar joint were scored by a rheumatologist (DL) who graded them according to the method of Kellgren and Lawrence (13). Written informed consent was obtained from all patients.

MRI evaluation. *Technique.* All MRI studies were performed no less than 24 hours and no more than 7 days before arthroscopic examination. Imaging was performed using a 1.5T scanner (General Electric Medical Systems, Milwaukee, WI) with a transmit–receive knee coil to achieve uniform receptivity throughout when the knee was in a neutrally rotated position. Synovial membrane was evaluated on a fast multiplanar spoiled gradient-recalled acquisition in the steady-state T1-weighted sequence (repetition time 180 msec, echo time 4.2 msec, flip angle 90°, field of view 12×12 cm, matrix 256×256 pixels, slice thickness 3 mm, slice gap 0.0 mm, and 1 acquisition) performed in a transverse plane without contrast agent. With the patient in the same position, 0.05 moles/kg of Gd-DTPA (Guerbet, Aulnay, France) was injected into a cubital vein and the sequence was repeated. Total acquisition time for the 2 sequences was 6 minutes and 12 seconds.

Synovial evaluation. Slices selected for grading of synovial membrane inflammation corresponded to the first and the last axial slices in which the patella was still visible. Synovial membrane inflammation was investigated in 5 regions of interest (ROIs) on axial postinjection T1-weighted sequences (Figure 1). These ROIs included 3 in the suprapatellar recess (lateral recess [ROI 1], medial recess [ROI 2], and just above the trochlear groove [ROI 5]) and 1 each in the lateral and medial femoral gutters (ROIs 3 and 4, respectively). The signal intensity of the inflamed synovium was high, but that of the fat tissue localized in the subintima was low (Figure 1). Thickening of the inflamed synovial membrane was determined in each ROI and graded on a 4-point scale (MRI synovial thickening grade) according to the Ostergaard classification: grade 0 = lack of enhancement of the synovial tissue (too thin to be seen on MRI, i.e., <100 μm); grade 1 = thickening of the synovial tissue by <2 mm; grade 2 = thickening of the synovial tissue

varying between 2 mm and 4 mm; grade 3 = synovial tissue >4 mm thick or nodular in pattern (Figure 2) (14). An MRI total score (the sum of the grades in each of the 5 ROIs) was calculated, giving a continuous variable between 0 and 15, with 0 corresponding to normal synovial tissue and 15 corresponding to the most severe and diffuse synovial inflammation.

In order to evaluate any relationship between synovial inflammation and nearby cartilage lesions, the medial ROI (medial recess and gutter) and the lateral ROI (lateral recess and gutter) of the synovial membrane were investigated when cartilage lesions were depicted in the same compartment. All ROIs were investigated when lesions were detected in the femoropatellar compartment. In order to assess interobserver variability, 2 observers (DL and IC-V) conducted all 39 examinations. One observer (DL) made 30 measurements twice to determine intraobserver reproducibility.

Arthroscopic examination. *Technique.* Just prior to arthroscopic examination of the knee, synovial fluid was removed from the joint and its volume was measured. Arthroscopy was performed by an orthopedic surgeon (DM) and a rheumatologist (DL) with the patient under local anesthesia (lidocaine adrenaline 2%). A standard knee arthroscope (2.7 mm) with a 30° fore oblique lens and a wide field of view was inserted via the inferior lateral and medial femorotibial portals. Arthroscopic exploration was combined with joint lavage. All procedures were recorded on VHS videotape (super VHS Panasonic VS 100H; Panasonic, Matsushita Electric Industrial, Osaka, Japan).

Evaluation of cartilage lesions. Chondral lesions were evaluated for each compartment of the knee during arthroscopic examination. First, chondral lesions were scored macroscopically according to Beguin and Locker's classification (15), in which grade 0 indicates normal cartilage, grade I indicates swelling and/or softening, grade II indicates superficial fibrillations, grade III indicates deep fibrillation down bone, and grade IV indicates exposure of the subchondral bone. Patients were then classified into 2 groups: group 1 exhibited mild chondral lesion(s) without any exposure of subchondral bone (early OA), corresponding to grades I and II in at least 1 of the 3 compartments of the knee, whereas group 2 exhibited severe cartilage lesion(s) with focal or diffuse exposure of subchondral bone (end-stage OA), corresponding to grades III and IV in at least 1 of the 3 compartments of the knee.

Second, a more defined evaluation was performed with an arthroscopic scoring system (the Société Française d'Arthroscopie [SFA] scoring system), taking into account not only the depth but also the localization and the extent of chondral lesions. In this scoring system, chondral lesions were recorded on a diagram of the knee. Reported information included the following: 1) location (medial femur and medial plateau, lateral femur and lateral plateau, patella and trochlear groove); 2) depth (based on the classification of chondropathy proposed by Beguin and Locker, see above); and 3) extent, involving 0–100% of the examined articular surface. The SFA total score was calculated as the sum of the data acquired for each knee compartment, i.e., the medial femorotibial compartment, the lateral femorotibial compartment, and the femoropatellar compartment. A maximum score of 200 in each compartment gave a total score ranging from 0 (normal cartilage in all articular surfaces of the knee) to 600 (complete absence of cartilage in all articular surfaces of the knee).
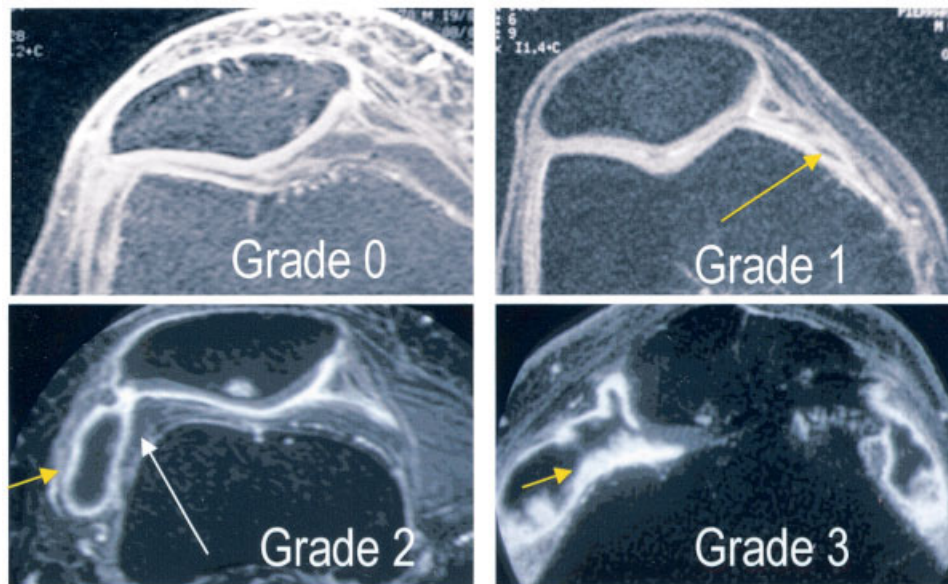
Figure 2. Magnetic resonance imaging (MRI) synovial thickening grades. Synovial thickening on postinjection T1-weighted sequences was evaluated according to the following grading system: grade 0 = lack of enhancement of the synovial tissue (too thin to be seen on MRI, i.e., <100 μm); grade 1 = thickening (linear enhancement) of the synovial tissue by <2 mm (**yellow arrow**); grade 2 = thickening of the synovial tissue varying between 2 mm and 4 mm (**yellow arrow**); grade 3 = thickening of the synovial tissue by >4 mm or nodular pattern (**yellow arrow**). Only the inflamed synovial membrane was enhanced by contrast agent, while the fat tissue stayed at low signal intensity (**white arrow**).

Synovial membrane evaluation. *Macroscopic scoring.* The joint cavity was carefully inspected paying particular attention to the 5 ROIs. The macroscopic appearance of the synovial membrane at each biopsy site was graded by an experienced arthroscopist (DM) as follows: grade 0 = no synovitis (translucent and slender villi formation); grade 1 = mild synovitis or fibrotic pattern (thin and opaque villi); grade 2 = moderate synovitis (opaque villi formation, thicker and more squat villi); grade 3 = severe synovitis (severe hypervascularization and proliferation). Where technically possible, synovial membrane biopsy specimens were obtained from the 5 ROIs using 2.7-mm biopsy forceps (Arthrex AR 2065; Arthrex, Naples, FL).

Microscopic scoring. Synovial samples were stored in formaldehyde and embedded in paraffin; 5-μm sections were cut and stained with hematoxylin and eosin for microscopic analysis. Stained sections were coded by an experienced histopathologist (JC) who was blinded to all data (MRI findings, stage of the disease, and biologic, chondroscopic, and macroscopic information). Synovial inflammatory activity was graded separately for each synovial sample. Six parameters were studied on at least 5 microscopic fields per section. Five of them were microscopy parameters classically used in inflammatory diseases: 1) number of synovial lining cells; 2) subsynovial infiltration by lymphocytes and plasma cells; 3) surface fibrin deposition; 4) congestion related to blood vessel vasodilatation and, to a minor degree, blood vessel proliferation; and 5) fibrosis (4,9). The last parameter, the perivascular edema frequently observed in OA biopsy samples but not depicted on normal synovial samples, was also studied. Each parameter was adapted as necessary for OA (changes are qualitatively similar to those seen in RA and SpA, but occur to a lesser degree) and scored as follows: 0 = none; 1 = mild; 2 = moderate; 3 = severe. Grade 0 corresponded to normal synovial tissue and grade 3 to the most severe pattern observed in OA samples. Finally, the average grading of the 6 parameters was calculated to give a mean total composite score for each biopsy specimen.

Statistical analysis. The characteristics of the 2 groups classified according to their arthroscopic features were compared using Wilcoxon nonparametric tests for continuous variables and Fisher's exact tests for qualitative variables. Spearman's rank correlation and Wilcoxon tests or Kruskal-Wallis tests were used to determine associations between biologic, histologic, clinical, and radiographic characteristics (r_s < 0.3 = little or no association; $0.3 \leq r_s \leq 0.7$ = moderate correlation; r_s > 0.7 = strong correlation). Inter- and intraobserver reliabilities of the MRI scoring systems were assessed with intraclass correlation coefficients (ICCs) and their 95% confidence intervals (95% CIs) and weighted kappa statistics. Associations between the MRI grades for synovial thickening and corresponding SFA scores and each microscopy parameter were tested with Spearman's rank correlation. Differences in MRI synovial thickening grade between the ROIs were tested with nonparametric Kruskal-Wallis tests.

Table 1. Baseline clinical data*

	Total population (n = 39)	Group 1 (n = 14)	Group 2 (n = 25)	P, group 1 vs. group 2
Age, years	56.41 ± 12.71	52.64 ± 16.30	58.52 ± 9.96	0.30
Men, %	43.58	35.71	48.00	0.46
VAS pain score, 0–100	51.26 ± 18.87	48.77 ± 18.24	53.06 ± 19.63	0.92
Lequesne's index, 1–25	10.66 ± 4.25	9.68 ± 3.95	11.26 ± 4.39	0.21
ESR, mm/hour	13.46 ± 16.93	10.38 ± 8.76	15.27 ± 20.27	0.67
CRP, mg/liter	6.08 ± 2.55	6.53 ± 3.16	5.78 ± 2.09	0.98
Presence of joint effusion, %	51.28	25.00	75.00	0.15
Synovial fluid volume, ml	6.03 ± 9.29	4.07 ± 8.30	7.22 ± 9.83	0.22
K/L grade				
Most affected femorotibial compartment	2.18 ± 1.31	1.62 ± 1.19	2.52 ± 1.29	0.04
Femoropatellar joint	2.06 ± 1.54	1.31 ± 1.65	2.52 ± 1.29	0.04

* Except where indicated otherwise, values are the mean ± SD. Thirty-nine patients were classified into 2 groups. Group 1 had mild chondral lesions without exposure of the subchondral bone at any cartilage surface of the knee, and group 2 had severe cartilage lesions with focal or diffuse exposure of subchondral bone. VAS = visual analog scale; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; K/L = Kellgren/Lawrence.

RESULTS

Characteristics of patients. Clinical, biologic, and radiographic data are summarized in Table 1. Findings were similar between patients assigned to group 1 (n = 14) and group 2 (n = 25). Joint effusion was observed in 51% of the total population, with a mean ± SD volume of 6.03 ± 9.29 ml; no significant difference was seen between the groups. Interestingly, there was a slight but statistically significant correlation between the volume of joint effusion and Lequesne's index (r_s = 0.34, P = 0.04), but not between the volume of joint effusion and the VAS pain score (r_s = 0.2, P = 0.13). A slight but

significant correlation was also noted between Lequesne's index and ESR (r_s = 0.42, P < 0.01). Moderate correlations were noted between the VAS pain score and ESR (r_s = 0.65, P < 0.006) and between the VAS pain score and serum CRP level (r_s = 0.42, P < 0.02). The severity of femorotibial radiographic findings was correlated with ESR (r_s = 0.41, P < 0.03), but not with either femoropatellar observations or CRP level.

Cartilage evaluation. The results of arthroscopic examination of cartilage lesions in the 3 compartments of the knee are summarized in Table 2. As expected, SFA scores differed significantly between the groups.

Table 2. Arthroscopic, magnetic resonance imaging (MRI), and macroscopic and microscopic data*

	Total population (n = 39)	Group 1 (n = 14)	Group 2 (n = 25)	P, group 1 vs. group 2
SFA score, 0–600	143.97 ± 90.88	63.83 ± 55.66	170.30 ± 80.09	0.0007
MRI synovial evaluation				
MRI grade, 0–3	1.55 ± 0.90	1.56 ± 0.86	1.55 ± 0.94	0.98
MRI total score, 0–15	7.51 ± 3.82	7.21 ± 3.68	7.68 ± 3.96	0.70
Macroscopic evaluation, 0–3	1.45 ± 0.69	1.32 ± 0.77	1.52 ± 0.64	0.30
Microscopic parameters, 0–3				
Synovial lining cells	1.72 ± 0.55	1.73 ± 0.57	1.72 ± 0.54	0.98
Fibrin deposition	0.42 ± 0.84	0.09 ± 0.29	0.58 ± 0.97	0.009
Fibrosis	1.65 ± 1.23	1.42 ± 1.30	1.76 ± 1.19	0.21
Edema	1.51 ± 1.11	1.42 ± 1.25	1.55 ± 1.05	0.67
Congestion	1.22 ± 0.87	1.06 ± 1.05	1.30 ± 0.78	0.14
Infiltration	1.46 ± 0.78	1.16 ± 0.72	1.59 ± 0.77	0.02
Mean total composite score	1.33 ± 0.53	1.14 ± 0.55	1.42 ± 0.51	0.02

* Values are the mean ± SD. The Société Française d'Arthroscopie (SFA) score was used to evaluate cartilage lesions for depth, localization, and extent for each articular surface. In MRI, synovitis was studied according to the MRI grade (synovial thickening for each region of interest [ROI]) and MRI total score (the sum of the grades for the 5 ROIs). See Patients and Methods for description of ROIs. Macroscopic and microscopic parameters were also studied in the total population and in groups 1 and 2 (see Table 1 for description of groups).

Table 3. Data regarding localization of cartilage lesions in each compartment of the knee*

Localization of cartilage lesions	Total population (n = 39)	Group 1 (n = 14)	Group 2 (n = 25)
Absence of cartilage lesions	5.0	14.3	0.0
Cartilage lesions localized in 1 compartment			
Medial femorotibial compartment	20.5	7.1	23
Lateral femorotibial compartment	7.5	14.2	4.0
Femoropatellar compartment	7.5	7.1	4.0
Total	35.5	28.4	31
Cartilage lesions localized in 2 compartments			
Medial femorotibial and femoropatellar compartments	18.0	21.4	16
Lateral femorotibial and femoropatellar compartments	13.0	14.2	11.4
Medial and lateral femorotibial compartments	5.5	14.2	0.0
Total	36.5	49.8	27.4
Cartilage lesions localized in all 3 compartments	23.0	7.5	41.6

* Values are the percent of patients. Localization of cartilage lesions was determined by the Société Française d'Arthroscopie score, which takes into account not only the depth of the chondral lesions but also their localization and their extent for each articular surface. See Table 1 for description of groups.

Data concerning localization of cartilage lesions in each compartment of the knee are summarized in Table 3. Lesions were limited to 1 compartment in 35.5% of the total population, in 28.4% of group 1, and in 31% of group 2. Lequesne's index and VAS pain scores did not differ between the groups; however, SFA scores correlated slightly with Lequesne's index ($r_s = 0.41, P < 0.01$), but not with VAS pain findings. The SFA score was slightly but significantly correlated with ESR ($r_s = 0.38, P < 0.020$), but not with CRP level ($r_s = 0.24, P = 0.16$).

MRI evaluation of the synovial membrane. *MRI analysis.* In the total population, the mean ± SD MRI synovial thickening grade (range 0–3) was 1.55 ± 0.90, and the mean ± SD MRI total score (range 0–15) was 7.51 ± 3.82, with no significant differences between the groups (Table 2). Interobserver reproducibility was excellent for the MRI total score (ICC 0.90, 95% CI 0.83–0.95) and good for the MRI grade (weighted $\kappa = 0.65$, 95% CI 0.54–0.75). Intraobserver reproducibility for the MRI total score was excellent (ICC 0.96, 95% CI 0.92–0.98).

Relationship between MRI score and clinical and biologic data. MRI synovial thickening grade and MRI total score were not statistically significantly associated with Lequesne's index or VAS pain score. MRI synovial thickening grade and MRI total score correlated slightly with ESR ($r_s = 0.44, P < 0.008$ and $r_s = 0.53, P < 0.001$, respectively), to a greater extent than with CRP level ($r_s = 0.19$ and $r_s = 0.32$, respectively). The MRI synovial thickening grade was poorly correlated with the severity of the cartilage lesions in the lateral femorotibial compartment and in the femoropatellar compartment ($r_s = 0.25, P = 0.06$ and $r_s = 0.65, P = 0.67$, respectively), but

a better association was seen in the medial femorotibial compartment ($r_s = 0.43, P = 0.007$).

Localization of inflammation. No statistically significant differences in MRI synovial thickening grade were observed between the different regions of the knee. No difference was observed between the upper (ROIs 1–3) and lower (ROIs 4 and 5) areas of the femoropatellar joint, or between the medial (ROIs 2 and 4) and lateral (ROIs 1 and 5) parts of the femorotibial joint (1,3).

Proximity of synovial inflammation and cartilage lesions. The MRI synovial thickening grade in the medial ROI (ROIs 2 and 4) correlated slightly with the severity of the cartilage lesions as reflected in the medial femorotibial SFA score ($r_s = 0.49, P = 0.001$). However, the MRI synovial thickening grade of the lateral ROI (ROIs 1 and 5) did not correlate with the severity of the cartilage lesions according to the lateral femorotibial SFA score ($r_s = 0.007$). The femoropatellar SFA score did not correlate with the MRI synovial thickening grade ($r_s = -0.08, P = 0.3$).

Correlation between MRI synovial thickening grade and macroscopic and microscopic findings. The correlations between MRI synovial thickening grade and macroscopic or microscopic data were established exclusively on ROIs in which synovial biopsies had been performed. Thus, MRI grade correlated well with macroscopic analysis ($r_s = 0.58, P < 0.001$). With regard to microscopy parameters, the correlation was statistically significant for infiltration ($r_s = 0.46, P < 0.0001$), congestion ($r_s = 0.30, P < 0.005$), fibrosis ($r_s = 0.31, P < 0.006$), synovial lining cells ($r_s = 0.23, P < 0.007$), and surface fibrin deposition ($r_s = 0.12, P < 0.01$), but
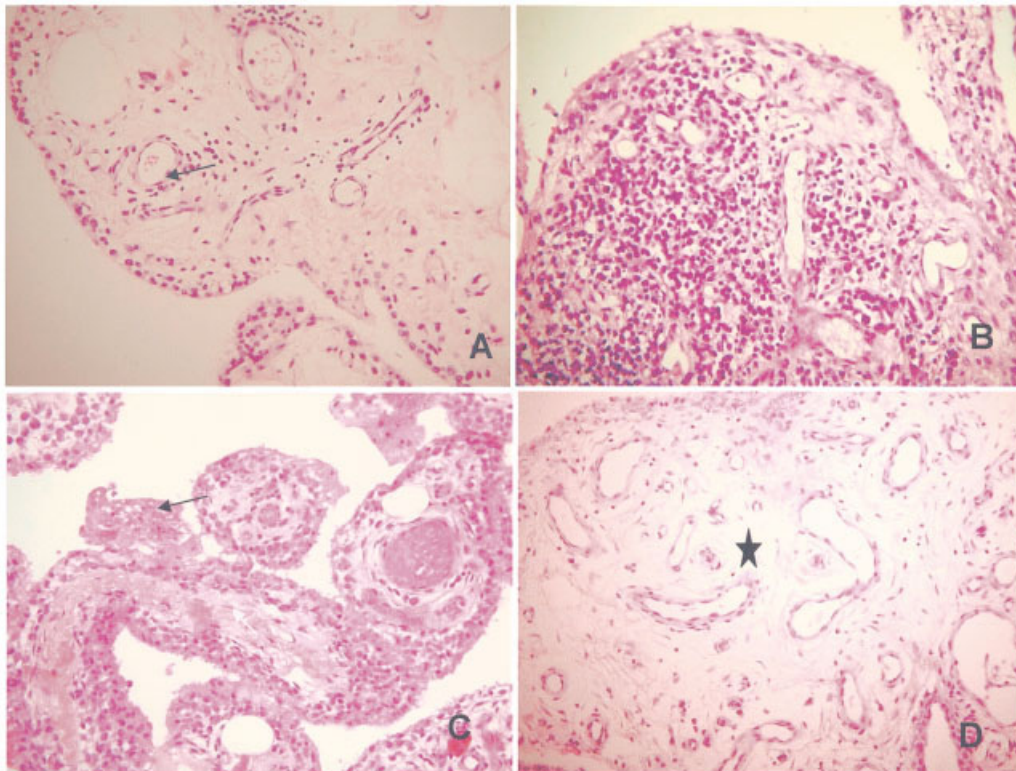
Figure 3. Microscopic features of the osteoarthritic (OA) synovial membrane. **A,** Normal synovial membrane composed of 2–3 layers of synovial lining cells (hematoxylin–eosin–saffron staining). Beneath them are localized capillaries (**arrow**) and fat tissue of the subintima. Note that infiltration is moderate. **B,** Severe infiltration of the subintima without an increase in the number of lining cells. **C,** Surface fibrin deposition is shown (**black arrow**), while the subintima of the villi is fibrotic (**white arrow**). **D,** Edema (**star**), synovial lining cells, and vascularization were often increased in OA synovial membrane biopsy samples but were not specific for disease severity. (Original magnification × 200.)

not for edema ($r_s = 0.17$, $P = 0.07$). Correlation with the mean total composite score was better ($r_s = 0.41$, $P < 0.0001$).

Macroscopic and microscopic patterns of the synovial membrane. Macroscopic and microscopic findings were not associated with Lequesne's index, the VAS pain score, or serum CRP level. ESR was slightly but significantly correlated with the microscopic characteristics of the synovial membrane ($r_s = 0.34$, $P = 0.047$), but not with the results of macroscopic evaluation. The correlation between the results of macroscopic evaluation and the mean total composite microscopy score was slight but significant ($r_s = 0.34$, $P < 0.045$). Among the 107 synovial samples studied (n = 34 in group 1, n = 73 in group 2), fibrin and infiltration parameters were more important in group 2 ($P = 0.009$ and $P = 0.015$, respectively). The degree of inflammation did not differ significantly between the ROIs studied, regardless of which microscopy parameter was considered. The mean total composite microscopy score was higher in group 2 than in group 1 ($P = 0.02$). The presence of exposed subchondral bone did not seem to affect the other microscopy parameters (fibrosis, synovial lining cells, congestion, and edema) (Figure 3).

DISCUSSION

The aim of this study was to evaluate the macroscopic and microscopic features of the synovial membrane and to determine whether the degree of synovial inflammation is influenced by subchondral bone exposure. Previous studies have clearly shown that OA synovial samples are characterized by a trend toward lower cell density, but that the proportions, distribution, and organization of the various cell populations are similar to those observed in RA or SpA (6,9,16). The 107

synovial samples analyzed here were therefore assessed using scales specifically adapted for OA. The analysis revealed that fibrin and infiltration parameters were more severe and related to disease severity, but no such difference was noted in other parameters. These results are in accord with Lindblad and Hedfors' suggestion that cellular infiltration results from chronic and acute phenomena in the synovial tissue (17). Surface fibrin deposition is mainly related to acute inflammatory processes and would provide a more specific reflection of disease severity.

Interestingly, the present findings revealed no difference between the groups in terms of fibrosis or the number of lining cells, both of which are classically associated with disease evolution and joint damage (3). Fibrosis is not necessarily only a scarring or repair mechanism as classically observed in end-stage disease; it may also be a dynamic phenomenon involving mediators that can stimulate fibroblast proliferation from the onset of OA (6). As a result, the mean total composite microscopy score was slightly higher in end-stage disease. Worsening of the histologic score with increasing disease severity in patients with degenerative joint disease (n = 11) and inflammatory joint disease (n = 11) was reported by Gibson et al (18). The ROIs studied here differed in synovial inflammation, but no significant variations in microscopy parameters were observed.

These results contrast with those of Hutton et al, who reported that synovial samples from the femoropatellar region exhibited prominent fibrosis and fibrin deposition, whereas those from the femorotibial compartment were characterized by greater inflammation, pigmentation, vascularity, fragment deposition, and hyperplasia. In that study, synovial biopsies were performed on 11 subjects with inflammatory diseases but on only 5 OA patients (19). Limitations of our microscopic study include failure to immunostain and characterize cell infiltration on synovial sections (neither of which was an initial objective). Furthermore, the effects of local and systemic treatment were not evaluated despite the evidence that antirheumatic drugs affect synovial histology (20–22). These issues should be considered in future studies.

MRI has the potential to characterize chondral lesions, to measure the loss of cartilage volume (23–27), to depict bone marrow edema (28), and to evaluate synovial membrane inflammation (9). All of these features are well established in OA, although the precise chronology of these events remains unknown. MRI may also contribute to a better understanding of clinical symptoms in OA (28–30). We showed that the volume of joint effusion was associated with Lequesne's index but not with the VAS pain score. With regard to proton-density sequences, Hill demonstrated in a large cohort of 458 subjects that moderate and large effusions with capsular distension and synovial thickening were significantly more common among OA subjects with than among those without knee pain. However, no functional evaluation was made in that study (29). We showed that the severity of disease and the degree of synovial inflammation on MRI (or in macroscopic and microscopic data) were no more than moderately correlated with the clinical index or with pain. ESR alone (not CRP level) exhibited a significant correlation with disease severity, MRI score, and microscopic data. The lack of correlation between the CRP level and these parameters was probably due to the low sensitivity of the CRP assay method used in this study. These results were not surprising, since Ostergaard et al had reported that swollen knee joints and/or tenderness were not associated with synovial membrane volume as measured by post–Gd-DTPA T1-weighted MR imaging, with macroscopic grading, or with any of the histologic grades in RA except surface fibrin deposition (9).

Inflammation of the synovial tissue has often been studied in RA and SpA using postcontrast T1-weighted MRI sequences. However, only 1 study has been performed in OA (involving 25 subjects scheduled for total knee replacement) (9), and 3 have been performed using MRI sequences without contrast agent (7,29,30). Neither intra- nor interobserver reliability was reported (30). In OA of the knee, Hill noted that the presence of synovial thickening measured using proton-density sequences was increasingly likely with increasing Kellgren/Lawrence grades. Intraobserver reproducibility of Hill's measurements was good (ICC 0.77) (29). It is important to note that synovial thickening was measured on sequences in which active synovitis could not be differentiated from the fat tissue present in the subintima. Only Gd-DTPA–enhanced T1-weighted sequences had the documented ability to enable quantification of inflamed synovium (synovial volume and rate of synovial enhancement on dynamic sequences), resulting in a good correlation with macroscopic and microscopic scores in RA and in SpA (8,31–37).

To our knowledge, this is the first cross-sectional investigation of an MRI-based quantitative scale of synovial inflammation in OA. We studied 39 OA-affected knees, with >100 OA synovial biopsies performed, evaluated at different stages of disease. Even though the MRI synovial thickening grade was well correlated with fibrosis, congestion, infiltration, and the

mean total composite microscopy score, our results must be interpreted with caution in light of the small number of patients studied.

With regard to RA, Ostergaard et al reported significant correlations between synovial membrane volume and histologic score, with the same range of values as in the present study (from $r_s = 0.59$ for surface fibrin deposition to $r_s = 0.22$ for edema [9]). The technique described here, as used in 5 ROIs, allows for exploration of synovial inflammation in the lateral and medial femorotibial compartments and in the femoropatellar compartment. Use of this approach demonstrated that synovial inflammation is more diffuse than presumed, with no significant differences between the ROIs. The results did not confirm those of Lindblad and Hedfors, who reported that arthroscopy showed inflammatory activity to be confined to the area surrounding cartilage lesions and that the least active areas were those furthest from cartilage lesions (17). It is important to emphasize that only 1 of the 12 subjects had OA in the study by Lindblad and Hedfors. In the present study, the only significant association observed was between synovitis in the medial recess and gutter and cartilage lesions in the same compartment. The findings suggest that cartilage lesions in the medial femorotibial compartment are alone in being crucial for the initiation and propagation of synovitis. The scoring system based on synovial thickening measured by postinjection T1-weighted sequence MRI, as described here, can easily be used by any rheumatologist and allows grading of inflamed synovial tissue with excellent intra- or interobserver reproducibility. The 5 ROIs are easily identified and can be scored in <10 minutes.

In conclusion, this is the first investigation to confirm the presence of synovitis in OA patients with chronic joint effusion and lack of response to corticosteroid injection or general treatment. The scale described can be applied without elaborate software or computer systems and has excellent intra- and interobserver reproducibility. Other than infiltration and fibrin parameters, which were more pronounced in end-stage disease, synovitis may be present from the onset of OA disease and may contribute to the worsening of chondral lesions. The MRI synovial thickening score correlates well with microscopy parameters; it could be used to classify people with OA in clinical trials and to help identify patients who might benefit from synovium-targeted drugs. A reliable measure of joint inflammation could be useful in clinical trials as a marker of therapeutic response and in clinical practice as a guide to treatment strategy.

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