The use of MRI in early inflammatory arthritis

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The Course of Bone Marrow Edema in Early Undifferentiated Arthritis and Rheumatoid Arthritis A Longitudinal Magnetic Resonance Imaging Study at Bone Level

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Abstract

Objective
In patients with rheumatoid arthritis (RA), bone marrow edema (BME) scores are associated with development of erosions. However, little is known about the course and outcome of BME at bone level. We undertook this study to determine the association of BME and synovitis with the development of erosions in the same bone longitudinally.

Methods
Using 1.5T magnetic resonance imaging at baseline and at 4- and 12-month follow-up, we studied 1,947 bones of the metacarpophalangeal, wrist, and metatarsophalangeal joints in 59 patients presenting with RA or undifferentiated arthritis. Scanning and scoring of BME, synovitis, and erosions were performed according to the Outcome Measures in Rheumatology Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system. We evaluated the relationship of the course of BME and synovitis with erosive progression at bone level during 1 year.

Results
Of the bones showing BME at baseline (n = 203), BME persisted in 56%, disappeared in 39%, and disappeared and then reappeared in 5%. Stratified analyses at baseline revealed that BME was associated with erosive progression both in the presence and in the absence of local synovitis, with odds ratios (ORs) of 7.5 (95% confidence interval [95% CI] 3.8-14.9) and 6.9 (95% CI 1.9-25.6), respectively. However, local synovitis was not associated with erosive progression in the presence or in the absence of BME (ORs of 2.0 [95% CI 0.6- 7.0] and 1.9 [95% CI 0.8-4.1], respectively). In multivariable generalized estimating equation analyses, persistent BME was strongly associated with erosive progression (OR 60.5 [95% CI 16.8-218.1]) in contrast to persistent synovitis (OR 1.3 [95% CI 0.4-4.4]).

Conclusion
BME frequently persists during the first year. Persistent BME was strongly associated with erosive progression in the same bone, independently of local synovitis. No independent association was observed for persistent synovitis. These findings are relevant for comprehending the development of erosions in RA.

Introduction

Inflammation of joints is the hallmark of rheumatoid arthritis (RA). Traditionally, joint inflammation is assessed by physical examination. However, modern imaging techniques, such as Doppler ultrasound and magnetic resonance imaging (MRI), are increasingly used to evaluate joints for the presence of local synovitis. Of these, MRI is the only modality that is able to depict bone marrow edema (BME) in addition to synovitis and tenosynovitis. Several histologic studies of BME lesions have shown that these lesions contain lymphocytic infiltrates; therefore, BME in RA is also called osteitis.[1–3] The interest in BME has been further increased by several studies which clearly showed that total BME scores are associated with erosive progression.[4–8]

Although the association between BME and erosive progression in RA is evident, the course of BME lesions is largely unknown. To our knowledge, it has never been investigated thoroughly how frequently BME lesions disappear, are "waxing and waning," or are persistently present over time in patients with newly diagnosed RA. In addition, the relationship between the course of BME over time and the development of erosions at bone level has not been explored.

Furthermore, BME and synovitis are often present simultaneously, and it is unclear to what extent the presence and course of BME, synovitis, or both markers of inflammation precede the development of local erosions. Reported studies on this topic performed multivariable analyses, mostly on the patient level, and showed that BME scores,[4,5,7–13] synovitis scores,[14–16] or both[6,17–19] were associated with radiographic progression. Stratification provides insights that are useful for disentangling the effects of related risk factors on an outcome; stratification also does not involve the assumptions underlying multivariable regression analysis. To our knowledge, stratified analyses at bone level that evaluate the risk attributed to BME lesions for developing erosions, both in the absence and presence of synovitis, have not been performed thus far.

We aimed to answer 3 questions. First, what is the course of individual BME lesions over time? Second, is the course of BME associated with erosive progression in the same bone? Finally, is the association between the presence or persistence of BME and erosive progression different when local synovitis is absent or present? To address these study questions, we performed serial MRIs of hand and foot joints and performed analyses at bone level.

Patients and Methods

Patients

We studied patients included in the Leiden Early Arthritis Clinic cohort, which is an inception cohort that includes consecutive patients with arthritis confirmed by physical examination and with symptom duration of <2 years. The cohort was started in 1993 and has been extensively described elsewhere.[20] From August 2010 onward, patients voluntarily underwent MRI at baseline. According to the study protocol, MRIs were repeated at 4 and 12 months in patients with RA or undifferentiated arthritis (UA; not fulfilling the criteria for RA or for other diagnoses)

at baseline. RA in this study was defined according to the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria.[21] It was considered appropriate to include UA patients as we hypothesized that the association between the presence or persistence of BME and erosive progression was not dependent on whether patients achieved a total score of ≥6 on the 2010 classification criteria for RA at baseline.[22,23] Fifty-nine patients who underwent serial scans during the first 12 months of their disease were studied. Of these 59 patients, 26 fulfilled the 2010 classification criteria for RA at baseline and 33 were classified as having UA. Disease-modifying antirheumatic drugs (DMARDs) were started in 46 patients (78%) during the first year; these included methotrexate (n = 36), sulfasalazine (n = 2), hydroxychloroquine (n = 5), prednisolone (n = 2), and tocilizumab in a trial setting (n = 1). The median interval between inclusion and the first MRI was 0.7 weeks. Written informed consent was obtained from all patients. The study was approved by the local medical ethics committee.

MRI

MRI of the second through fifth metacarpophalangeal (MCP), wrist, and metatarsophalangeal (MTP) joints was performed on the most painful side or, in the case of symmetric symptoms, on the dominant side. Follow-up MRIs were performed on the same side that was scanned at baseline. MRI was performed using an MSK Extreme 1.5T extremity MR imaging system (GE Healthcare). In the hand, the following sequences were acquired before contrast agent injection: T1-weighted fast spin-echo (FSE) sequence and T2-weighted FSE sequence with frequency-selective fat saturation in the coronal plane. After intravenous contrast injection, T1-weighted FSE sequences with frequency-selective fat saturation in the coronal and axial plane were obtained. The forefoot was scanned using a T1-weighted FSE sequence in the axial plane and a T2-weighted FSE sequence with frequency-selective fat saturation in the axial plane. Due to time constraints, MRI of the foot was only done before contrast agent injection. A more detailed description of the scan protocol is available upon request from the corresponding author.

MRI scoring

MRIs were scored for BME, synovitis, and erosions according to the Outcome Measures in Rheumatology Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) system.[24] Briefly, BME is scored from 0 to 3 based on the volume of edema (0%, 1-33%, 34-66%, 67-100% of edematous bone), synovitis is scored from 0 to 3 (none, mild, moderate, severe), and erosions are scored from 0 to 10 based on the proportion of eroded bone (from 0% to 91-100%).[24] One reader (WPN) who was trained and experienced in scoring according to the RAMRIS system (.1,000 MRIs for several projects) scored all MRIs for each patient. The reader was blinded to any clinical data but not to the order in which the scans were made, since scoring scans in chronological order is the most sensitive method for detecting progression.[25,26] The intrareader intraclass correlation coefficient (ICC) for total RAMRIS baseline scores was 0.93, determined from 27 baseline readings scored twice, and the intrareader ICC for scoring progression was 0.98, determined from the total progression scores of 5 series of scans that were scored twice.

Analyses were performed at bone level. A total of 1,947 bones (33 bones [10

at MTP joints, 8 at MCP joints, and 15 at wrist joints] in 59 patients) could be scored for BME and erosions at 3 time points, resulting in a maximum of 5,841 observations. A total of 708 joints could be scored for synovitis (12 joints [MTP joints 1-5, MCP joints 2-5, distal radioulnar joint, radiocarpal joint, and intercarpal plus carpometacarpal joints] in 59 patients), resulting in a maximum of 2,124 observations. Seven patients did not undergo an MRI at 4 months because of a temporary breakdown of the MRI scanner (this concerned 231 bones and 84 joints). Twenty bones could not be scored due to being located outside the field of view, and 6 bones were missing due to an amputated hallux (3 joints) in 1 patient. Additionally, 64 bones and 31 joints could not be reliably evaluated for BME and synovitis, respectively, due to inhomogeneous fat suppression. A total of 257 observations on erosions (4.4%), 321 observations on BME (5.5%), and 118 observations on synovitis (5.6%) were missing. All these missing data were regarded as missing completely at random (assuming no association between missingness and patient characteristics or outcome) and were not imputed.

MRI data were dichotomized according to predefined cutoffs. Bones with a score of ≥1 were considered positive for BME. Joints with a score of ≥1 were considered positive for synovitis. Erosive progression was defined as an increase in erosion score of ≥1 between baseline and year 1. BME and erosive progression were studied at bone level. To study local synovitis, the joint(s) surrounding the bone was assessed. For the bones of the MTP and MCP joints, this concerned simply the local joint. For the carpal bones (including the metacarpal bases), local synovitis was considered present when the score for synovitis was ≥1 in the radiocarpal or intercarpal joint. For the distal ulna and radius, local synovitis was also considered present if the distal radioulnar joint had a score of ≥1. These choices were made because the wrist joints surround several bones, and synovitis is generally not confined to the part of the joint located next to certain bones. Subsequently, the dichotomized scores for BME and synovitis for each bone at each time point were summarized in patterns. For example, a bone with BME only at baseline was labeled as 1-0-0, while a bone with BME at baseline and 1 year but not at 4 months was labeled as 1-0-1. Next, we counted the number of MRIs per bone that showed BME or synovitis and called this the “load” of BME or local synovitis. Therefore, for a bone with the pattern 1-0-0 the load is 1, while for a bone with the pattern 1-0-1 the load is 2.

Sensitivity analyses
Although we anticipated that the association between local inflammation and erosive progression was comparable in patients who at first presentation were classified as having RA or UA, analyses were repeated in the subgroup of RA patients. Furthermore, dichotomization of MRI data was also done with a cutoff of ≥2.

Statistical analysis
Pearson’s chi-square test (or Fisher’s exact test when appropriate) was used for analyses of baseline MRI data. Spearman’s rank correlation was used for (partial) correlation analyses. Associations of BME and synovitis (both at baseline and course over time) with erosive progression were analyzed using logistic regression with generalized estimating equations (GEEs), which allowed adjusting

for correlations of bones and joints within patients. The exchangeable correlation structure was used. P values less than 0.05 were considered significant. Odds ratios (ORs) are presented with 95% confidence intervals (95% CIs). SPSS software version 20.0 (IBM) was used.

Results

Baseline characteristics

Baseline characteristics of the 59 patients are presented in Table 1. At disease presentation, BME was present in 239 bones (12%), and synovitis was observed in surrounding joints at 825 bones (43%).

Table 1 Baseline characteristics of the patients with early UA and RA*

Variable	All (N=59)	RA (N=26)	UA (N=33)
Age, mean (sd) years	57.2 (14)	58.5 (10)	56.1 (16)
Women, no (%)	31 (53)	14 (54)	17 (52)
Symptom duration, weeks†	16.7 (9-26)	20.9 (13-34)	12.5 (7-25)
Time to MRI, weeks‡	0.7 (0.1-1.7)	0.8 (0-2.1)	0.7 (0.1-1.4)
TJC (68 joints)	4 (2-8)	6 (4-9)	3 (2-4)
SJC (66 joints)	3 (2-6)	5 (2-7)	3 (1-4)
CRP (mg/L)	4 (3-13)	5 (3-18)	4 (3-11)
ACPA positive, no (%)	22 (37)	18 (69)	4 (12)
Fulfilled 2010 RA classification criteria, no. (%)	26 (44)	26 (100)	0 (0)
Total RAMRIS score	12 (7-22)	12 (8-25)	11 (6-21)
Total BME score	3 (1-6)	5 (2-8)	2 (1-5)
Total synovitis score	5 (1-8)	4 (1-7)	6 (2-9)
Total erosion score	4 (2-7)	5 (2-7)	3 (2-7)
Change in total RAMRIS score, baseline-12-month follow-up	-2 (-9-1)	0 (-9.3-5)	-3 (-8.5-1)
Change in BME score, baseline-12-month follow-up	0 (-2-1)	0 (-2.3-3)	0 (-1.5-1)
Change in synovitis score, baseline-12-month follow-up	0 (-3-1)	0 (-3-2.3)	-1 (-3-0)
Change in erosion score, baseline-12-month follow-up	0 (0-1)	1 (0-2.3)	0 (0-1)

* Except where indicated otherwise, values are the median (interquartile range).
UA=undifferentiated arthritis; RA=rheumatoid arthritis; TJC=tender joint count; SJC=swollen joint count; CRP=C-reactive protein; ACPA=anti–citrullinated protein antibody; RAMRIS=Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system; BME=bone marrow edema. † Time between onset of symptoms and inclusion in cohort. ‡ Time between inclusion in cohort and undergoing first magnetic resonance imaging (MRI).

Association of BME and synovitis at baseline with erosive progression
Erosive progression during the first year was present in 56 bones (3%) (locations of erosions are available upon request from the corresponding author); these 56 bones belonged to 29 patients, of whom 10 (34%) were positive for anti-citrullinated protein antibodies (ACPAs). First, we studied the association of baseline BME and synovitis with erosive progression (Table 2). Of 237 bones that scored positive for BME at baseline, 30 (13%) showed erosive progression. Bones with BME showed more frequent erosive progression than bones without BME (OR 9.7 [95% CI 5.6-16.8], P<0.001) (Table 2). Of all of the bones that were surrounded by synovitis, 41 (5%) showed erosive progression; bones with local synovitis had erosive progression more often than did bones without baseline synovitis (OR 3.8 [95% CI 2.1-7.0], P<0.001) (Table 2).

Baseline BME and local synovitis often occurred together; 197 bones with BME also had surrounding synovitis (82% of all bones with BME). Next, we performed stratified analyses to further explore the effects of BME and local synovitis. In the

Table 2 ORs for development of erosive progression at bone level during the first year, in the presence or absence of local synovitis or BME at baseline*

	Erosive progression			
	Yes	No	OR (95%CI)	p†
All data				
BME present	30	207	9.7 (5.6-16.8)	<0.001
BME absent	25	1667		
Synovitis present	41	783	3.8 (2.1-7.0)	<0.001
Synovitis absent	15	1098		
Stratification for synovitis				
Synovitis present				
BME present	27	169	7.5 (3.8-14.9)	<0.001
BME absent	13	612		
Synovitis absent				
BME present	3	38	6.9 (1.9-25.6)	0.016
BME absent	12	1054		
Stratification for BME				
BME present				
Synovitis present	27	169	2.0 (0.6-7.0)	0.26
Synovitis absent	3	38		
BME absent				
Synovitis present	13	612	1.9 (0.8-4.1)	0.12
Synovitis absent	12	1054		

* Local synovitis was defined as synovitis surrounding the bone of interest. For instance, when evaluating the distal head of the second metacarpal joint, synovitis within the second metacarpal joint was assessed. Of all 1,947 bones, 18 had missing bone marrow edema (BME) or erosion scores, 10 had missing synovitis or erosion scores, and 19 had missing BME, synovitis, or erosion scores. OR°odds ratio; 95% CI595% confidence interval. † Uncorrected for within-patient correlations.

absence of synovitis, presence of BME at baseline was associated with erosive progression (OR 6.9 [95% CI 1.9-25.6], P=0.016). Similarly, in the presence of synovitis, local BME was associated with erosive progression in the same bone (OR 7.5 [95% CI 3.8-14.9], P<0.001). Subsequently, the association between local synovitis and erosive progression was evaluated, showing that both in the presence and absence of BME, synovitis was not significantly associated with local erosive progression (OR 2.0 [95% CI 0.6-7.0], P=0.26 and OR 1.9 [95% CI 0.8-4.1], P=0.12, respectively) (Table 2).

Stratified analyses provided insights into the relationships between both risk factors and erosive progression. Because the stratified analyses did not take into consideration that multiple bones and joints could be involved in 1 patient, resulting in these observations not being completely independent, we subsequently performed a GEE analysis. When we analyzed the association of BME with erosive progression, a significant association was observed (OR 10.1 [95% CI 4.0-25.6], P<0.001). Univariable analysis of synovitis also showed a significant association (OR 5.2 [95% CI 2.0-13.2], P<0.001). When baseline BME and synovitis were analyzed together in 1 analysis, BME was strongly associated with erosive progression (OR 6.8 [95% CI 2.9-15.9], P<0.001), in contrast to a weaker association for synovitis (OR 2.5 [95% CI 1.2-5.3], P=0.02). To assess whether the presence of both synovitis and BME made an additive or multiplicative contribution to the development of erosive progression, an interaction term between BME and synovitis was also added in a separate model. This interaction term showed no significant effect (OR 0.5 [95% CI 0.1-2.4], P=0.54).

Course of BME and synovitis over time.
Next, we studied the course of BME assessed at baseline and at 4- and 12-month follow-up; this resulted in several patterns (Table 3). The large majority of bones (81%) had no BME at any point in time (pattern 0-0-0). The second most frequent pattern was 1-1-1, indicating that BME at baseline was also present at months 4 and 12. When BME was present at baseline, it remained present in 56% of bones (pattern 1-1-1), disappeared during follow-up in 39% of bones (patterns 1-1-0 and 1-0-0), and disappeared and reappeared in 5% of bones (pattern 1-0-1) (Table 3).

The course of MRI-detected synovitis was studied similarly. Synovitis was most often persistent when it was present at baseline (pattern 1-1-1, 75%). Disappearing patterns were present as well (pattern 1-0-0, 8%; pattern 1-1-0, 15%), and disappearing and reappearing patterns were infrequent (pattern 1-0-1, 3%) (Table 3).

Course of BME and synovitis and erosive progression.
Subsequently, we studied erosive progression in relation to the course of BME and synovitis. The 8 different patterns were summarized in 4 groups of loads reflecting the number of MRI scans for which a bone or joint was positive for BME or synovitis, respectively (for instance, the patterns 1-1-0, 1-0-1, and 0-1-1 were grouped as a load of 2, indicating that an MRI was positive 2 times for BME or synovitis). Erosive progression was infrequent when BME was absent in all 3 scans (0.2%) (Table 4). When BME was present at 2 or 3 time points, erosive progression was present in 19.2% and 15.2% of bones (Table 4). Similarly, erosive progression

Table 3 Patterns of BME in bones and local synovitis surrounding bones when magnetic resonance images were evaluated at baseline and after 4 and 12 months of follow-up*

Pattern†	No. of bones (% of total bones) ‡	Percent of total bones with baseline BME or baseline synovitis§	No. of bones with erosive progression (% per pattern)
BME			
0-0-0	1332 (80.9)	NA	3 (0.2)
0-0-1	58 (3.5)	NA	6 (10.3)
0-1-0	26 (1.6)	NA	3 (11.5)
0-1-1	28 (1.7)	NA	9 (32.1)
1-0-0	40 (2.4)	19.7	1 (2.5)
1-0-1	11 (0.7)	5.4	1 (9.1)
1-1-0	39 (2.4)	19.2	5 (12.8)
1-1-1	113 (6.9)	55.7	17 (15.2)
Synovitis			
0-0-0	839 (50.3)	NA	4 (0.5)
0-0-1	14 (0.8)	NA	0 (0)
0-1-0	14 (0.8)	NA	0 (0)
0-1-1	77 (4.6)	NA	10 (13)
1-0-0	57 (3.4)	7.9	1 (1.8)
1-0-1	19 (1.1)	2.6	2 (10.5)
1-1-0	105 (6.3)	14.5	2 (1.9)
1-1-1	543 (32.6)	75.0	27 (5)

* Local synovitis was defined as synovitis surrounding the bone of interest. For instance, when evaluating the distal head of the second metacarpal joint, synovitis within the second metacarpal joint was assessed. NA=not applicable.
† Pattern 1-0-0 indicates that this feature was present at baseline but not at 4 and 12 months (see Patients and Methods).
‡ The total number of bones sampled for bone marrow edema (BME) patterns was 1,647. The total number of bones sampled for synovitis patterns was 1,668.
§ The percent of total bones with baseline BME is shown only for BME patterns. The percent of total bones with baseline synovitis is shown only for synovitis patterns.

was most frequently present when synovitis was present at 2 or 3 time points (in 7% and 5% of bones, respectively) (Table 4).

Stratifying for all courses of BME and all courses of synovitis was not possible because it resulted in 64 (8x8) strata when evaluating patterns or 16 (4x4) different strata when evaluating loads, and these subgroups were too small. Some stratified analyses (for the load of synovitis within the bones with persistent BME) are available upon request from the corresponding author. To further increase our comprehension of the relationship of the courses of both BME and synovitis with erosive progression, we used partial correlation. The number of scans positive for BME (the load) was correlated with erosive progression (r_s=0.325, P<0.001). The load of synovitis was also correlated with erosive progression (r_s=0.133, P<0.001). In addition, the load of BME was associated with erosive progression

Table 4 Loads of BME in bones and local synovitis surrounding bones when magnetic resonance images were evaluated at baseline and after 4 and 12 months of follow-up*

Load†	Pattern‡	No. of bones (% of total bones) §	No. of bones with erosive progression (% per load or pattern)
BME			
0	0-0-0	1332 (80.9%)	3 (0.2%)
1	0-0-1, 0-1-0, 1-0-0	124 (7.5%)	10 (8.1%)
2	0-1-1, 1-0-1, 1-1-0	78 (4.7%)	15 (19.2%)
3	1-1-1	113 (6.9%)	17 (15.2%)
Synovitis			
0	0-0-0	839 (50.3%)	4 (0.5%)
1	0-0-1, 0-1-0, 1-0-0	85 (5.1%)	1 (1.2%)
2	0-1-1, 1-0-1, 1-1-0	201 (12.1%)	14 (7%)
3	1-1-1	543 (32.6%)	27 (5%)

* Local synovitis was defined as synovitis surrounding the bone of interest. For instance, when evaluating the distal head of the second metacarpal joint, synovitis within the second metacarpal joint was assessed.
† Number of scans positive for bone marrow edema (BME)/synovitis.
‡ Pattern 1-0-0 indicates that this feature was present at baseline but not at 4 and 12 months (see Patients and Methods).
§ The total number of bones sampled for BME loads and patterns was 1,647. The total number of bones sampled for synovitis loads and patterns was 1,668.

Table 5 ORs for the development of erosive progression in relation to load of BME and local synovitis during the first year of disease, corrected for within-patient correlations of features on magnetic resonance imaging*

		Univariable analysis		Multivariable analysis¶	
Load†	No. of bones (% of total bones) ‡	OR (95% CI)	P§	OR (95% CI)	P§
BME					
0	1332 (80.9%)	Reference		Reference	
1	124 (7.5%)	23.0 (8.6-62.0)	<0.001	19.3 (6.0-62.0)	<0.001
2	78 (4.7%)	66.4 (17.1-257.3)	<0.001	55.4 (13.0-235.5)	<0.001
3	113 (6.9%)	68.4 (20.9-223.9)	<0.001	60.5 (16.8-218.1)	<0.001
Synovitis					
0	839 (50.3%)	Reference		Reference	
1	85 (5.1%)	2.4 (0.2-24.4)	0.47	1.0 (0.1-9.8)	0.99
2	201 (12.1%)	10.7 (2.7-41.8)	<0.001	2.8 (0.8-9.5)	0.091
3	543 (32.6%)	11.0 (4.1-29.3)	<0.001	1.3 (0.4-4.4)	0.64

* Local synovitis was defined as synovitis surrounding the bone of interest. For instance, when evaluating the distal head of the second metacarpal joint, synovitis within the second metacarpal joint was assessed. OR=odds ratio; 95% CI=95% confidence interval.
† Number of scans positive for bone marrow edema (BME)/synovitis.
‡ The total number of bones sampled for BME loads was 1,647. The total number of bones sampled for synovitis loads was 1,668.
§ Corrected for within-patient correlations by generalized estimating equation analysis.

when adjusting for the load of synovitis using partial correlation (r_s 5 0.299, P<0.001). However, when the association between the load of synovitis and erosive progression was adjusted for the load of BME, significance was lost (r_s 5 20.004, P=0.89). This suggests that when controlling for the load of BME (i.e., with the variance explained by the load of BME), there is no significant correlation between the load of synovitis and erosive progression.

These partial correlation analyses did not adjust for within-patient correlations. GEE analyses were performed to account for this, showing statistical significance for the load of BME but not for the load of synovitis (Table 5). The OR for local erosive progression in case of persistent BME was 60.5 (95% CI 16.8- 218.1); in contrast, in case of persistent synovitis the OR was 1.3 (95% CI 0.4-4.4) (Table 5).

Findings of sensitivity analyses
Similar results were found when the latter GEE analyses were repeated in the subgroup of patients fulfilling the criteria for RA (further information is available upon request from the corresponding author). Similar results were obtained when we repeated the GEE analyses within the subgroup of patients treated with DMARDs (data not shown). Thus far, BME was considered present when a bone had a BME score of ≥1. We also explored using a score of ≥2 as a cutoff; we did the same for synovitis. However, the subgroups of patients with positive scores became small (further information is available upon request from the corresponding author), hampering further subanalyses.

Discussion

It was already known that the total burden of BME in patients with RA at the time of diagnosis (total BME score per patient) is associated with erosive progression.[4–6,8,11,12,19] The course of BME and synovitis at bone level and its association with erosive progression at the same location in patients with newly diagnosed RA has not been thoroughly studied thus far. We observed that when BME was present at disease presentation, it most often persisted during the first year and seldom disappeared followed by reappearing. Furthermore, we observed that persisting BME was strongly associated with erosive progression; this effect was independent of the effect of persistent synovitis. In contrast, persistent synovitis was not evidently associated with erosive progression independent of the presence of persistent BME.

The findings of this longitudinal study at bone level extend our comprehension of BME in RA. Since BME and synovitis frequently occurred together, stratified analyses were helpful for gaining insight into the relationship of BME and synovitis with erosive progression without the influence of assumptions such as the linearity assumption, which generally underlies multivariable regression analyses. Stratification showed that in the presence of baseline BME, baseline synovitis was not associated with erosive progression. Because stratification does not take into account the correlation between bones within a patient, GEE analyses were also performed. Overall, the results of stratified analyses, partial correlation analyses, and GEE analyses were fairly similar.

The present findings do *not* indicate that synovitis is not important for the development of erosions. The previously proposed inside-out or outside-in hypotheses for the development of erosions are not substantiated by our data.[27] Our measurements started at disease presentation and ended after 1 year of follow-up. It is possible that disease processes causing erosions (for instance, synovitis) are already active or transient in preclinical disease phases.[28,29] Since these phases were not studied, other studies are needed to further explore the role of local synovitis and BME in very early phases of disease in relation to erosion development.

The results of this study may have some implications for future clinical trials in which erosive progression is the outcome. Trials with treatments that aim to prevent erosive progression may benefit from the selection of patients with BME.

This study has several limitations. First, MRIs were scored in chronological order because this method has been proven to be sensitive.[25,26] A drawback of this choice is that this may have influenced the results to some extent; with this method, some detected erosions might have remained undetected if the scans had been scored in a blinded manner with regard to time sequence. Importantly, at the time of scoring, there was no a priori hypothesis as to whether BME or synovitis was associated differently with erosive progression. Second, we assessed the course of BME over time with 3 MRI scans during 1 year. However, BME and synovitis could disappear and/or appear in the time intervals between the scans. Had this been the case, BME or synovitis in RA would be less “persistent” or “absent” than suggested by the current data. We cannot exclude the possibility that serial scans with shorter intervals between the scans would show different results, but it was not feasible to perform scans more regularly.

Third, the number of patients included in this study was relatively small. Therefore, our study was insufficiently powered to perform subanalyses in ACPA-positive and ACPA-negative disease separately. We also had insufficient power to perform subanalyses with a higher cutoff of ≥2 for BME and synovitis, as these larger lesions were infrequent. We assume that similar results would have been obtained if only larger lesions were analyzed, but our data did not permit us to conclude this. A fourth limitation is that our MRI protocol did not contain sequences of the foot after the administration of contrast, which may have led to an underestimation of synovitis in the foot. In addition, higher resolution MRI sequences (e.g., 3-dimensional gradient-echo sequences) could have provided higher sensitivity for erosive progression.

Because “the wrist” contains 15 bones and 3 joints, choices were made to define local synovitis. We have repeated the analyses when it was defined as synovitis located in the synovium adjacent to the carpal bone only. This yielded comparable results (data not shown).

Treatment was not included in our analyses because we studied the association between MRI-detected inflammation and erosive progression. We hypothesized that treatment affects the level of inflammation but not the relationship between inflammation and destruction.[30] In other words, we assumed that treatments applied (conventional DMARDs) had no direct effect on erosive progression.

The relationship between location of inflammation and erosive progression was not evaluated. Although there are preferential locations for erosive progression (e.g., MTP joint 5 and MCP joint 2), this preference applies to both inflammation and erosive progression.[31] Therefore, we assumed that the association between inflammation and erosive progression was independent of location.

In conclusion, when BME was present at disease presentation, it frequently persisted at subsequent measurements during the first year. Persistent BME was strongly associated with erosive progression, both in the presence and absence of local synovitis. For persistent synovitis, no association with erosive progression independent of BME was observed. These findings increase our knowledge of the relevance of BME for erosive progression.

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