

REVIEW

Bone marrow edema and osteitis in rheumatoid arthritis: the imaging perspective

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Abstract

Magnetic resonance imaging bone marrow edema is an imaging feature that has been described in many conditions, including osteomyelitis, overuse syndromes, avascular necrosis, trauma, and inflammatory arthritides. In rheumatoid arthritis (RA), bone edema has special significance as it has been shown to be a common and widespread lesion that is often apparent at the hands and wrists but has also been described elsewhere, including the feet. It may occur in early or late disease and has been shown in several large cohort studies to have major negative implications for prognosis. It is the strongest predictor of erosive progression yet to be identified and characteristically occurs in those patients with the most aggressive and potentially disabling disease. In patients with undifferentiated arthritis, bone edema also predicts progression to criteria-positive RA, both independently and to a greater extent when combined with anti-cyclic citrullinated peptide status or rheumatoid factor positivity. Its histological correlate in the late stages of RA has been shown to be osteitis, in which the bone marrow beneath the joint is invaded by an inflammatory and vascular lymphoplasmacytic infiltrate. This lies adjacent to trabecular bone, where increased numbers of osteoclasts have been observed within resorption lacunae, suggesting a mechanistic link between inflammation and erosive bone damage. This could lead to erosion both of the overlying cortex, leading to classic radiographic rheumatoid erosions, and of local trabecular bone, possibly contributing to periarticular osteopenia and cyst formation. In addition to synovitis, osteitis is now regarded as a major rheumatoid lesion that is responsive to therapeutic intervention.

Introduction

Imaging has traditionally been regarded by rheumatologists as a clinical tool to help diagnose and monitor the progress of various rheumatic diseases. This utilitarian perspective continues to be relevant in 2012, but with the introduction of advanced modalities, imaging has recently assumed another and equally important role as a non-invasive means to investigate joint pathology. Traditionally, what we know of the pathology of rheumatoid arthritis (RA) from imaging has come from plain radiography. This has led to a rather skewed emphasis on cortical bone, which by virtue of its calcium content is very clearly depicted on plain x-ray (XR). Clearly, erosion of cortical bone is the *sine qua non* of aggressive RA, and from the radiographic point of view, the bone underlying the cortex is much less informative, revealing only a degree of periarticular osteopenia in active disease [1]. This may have contributed to the impression that rheumatoid bone was an inert scaffold, covered in most parts of the joint by hyaline cartilage (radiographically, a blank space) and surrounded and eroded by inflamed synovium (radiographically, soft tissue swelling). In a seminal study comparing joint histology from cadavers with post-mortem radiography, Resnick and Gmelich [2] provided the necessary 'proof' that the XR image of the joint was an accurate representation. Subsequent studies of the synovium, obtained via synovial biopsy and from surgical samples, were conducted from the 1970s to the 2000s by using increasingly sophisticated immunohistochemical techniques. These studies combined with radiography, as described above, resulted in the traditional view that the rheumatoid joint was attacked 'from the outside' by inflamed synovium, full of activated inflammatory cells releasing proinflammatory and bone-resorbing cytokines and thus 'burrowing down' through cartilage and bone to produce the rheumatoid erosion as summarized by Schett and Firestein [3].

Recently, this traditional view has been challenged, largely since the advent of magnetic resonance imaging (MRI) and its application to the imaging of RA. MRI provides a means to view the subchondral trabecular bone underneath the rheumatoid joint, an area that

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previously was largely invisible. Considerable evidence now suggests that rheumatoid erosions may also develop 'from the inside out,' and attention is now being paid to the subchondral bone as an important site of pathology [3]. This, in turn, has raised the question of whether the bone marrow could be implicated in this disease, with the alarming but exciting prospect that a complete conceptual overhaul is required. This article will review imaging data that shed light on this issue, including information from XR, MRI, and ultrasound (US) observational studies as well as recent randomized controlled trials.

MRI bone edema – common in inflammatory arthritis

The term 'bone marrow edema' (BME) was first used by Wilson and colleagues [4] in 1988 to describe bone marrow hyperintensities on T2-weighted (T2w) MRI images in patients with transient osteoporosis. However, use of the term 'edema' leaves much to be desired. It raises confusing questions in the clinician's mind about how edema could occur inside bone, a tissue that is clearly not distensible. What edema really means is 'tissue water' as the high T2w MRI signal is derived from protons in relatively free water molecules contained within cells (other than lipocytes) and blood vessels. These are concentrated in regions of inflammation, and for this reason, MRI scanning has become widely used for the detection of inflammatory lesions by using the sensitive T2W sequences where inflammation is detected as bright signal.

On T2w images, calcified cortical bone and trabecular bone appear as signal voids (black). The adjacent tissue, which in normal subchondral bone is usually marrow fat, generates signal and silhouettes the actual bone. Bony trabeculae themselves are very small and difficult to see on two-dimensional spin echo sequences, including short tau inversion recovery (STIR) images. They are better delineated by using three-dimensional gradient echo techniques, but these sequences are susceptible to magnetic field heterogeneities. Fat saturation can be achieved by the MRI scanner, resulting in loss of T2w bright signal from marrow fat, so that the overall appearance of subchondral bone is dark gray or, more correctly, 'low signal' on T2w fat-saturated (T2FS) and STIR images. When fat is replaced by inflammatory tissue, or any tissue containing more free water than fat, the signal on T2FS becomes bright. The corollary of this on the T1w image is that the bony cortex has low signal and normal underlying trabecular bone containing fat has high signal. Increased water or BME on this sequence is seen as a low-signal region beneath the cortex which will enhance with contrast if it is vascular [5] (Figure 1).

MRI BME occurs in many conditions [6]. Florid BME with intense bright signal on T2w or STIR sequences is typical of osteomyelitis [7,8]. In this situation, histology is

well documented and an active inflammatory osteitis replaces the normal marrow fat [7]. BME is also an important early feature of sacroiliitis occurring in the spondyloarthropathies. Appel and colleagues [9] described a small series of eight ankylosing spondylitis patients in whom bone biopsy was taken from the zygapophyseal joints and histological examination revealed osteitis corresponding to regions of MRI BME. BME has also been described in psoriatic arthritis [10], in which it may be associated with dactylitis [11], enthesitis, and especially arthritis mutilans [12]. In osteoarthritis, BME lesions are somewhat different histologically, featuring marrow fat necrosis, fibrosis, and healing trabecular microfractures as described by Zanetti and Taljanovic [13,14]. Thus, MRI BME is not disease-specific. There is a parallel with the radiographic sign of osteopenia, which may be associated with osteomalacia, osteoporosis, or, in its localized periarticular form, RA. However, BME has been found to have special significance in RA, not only as an indicator of joint inflammation but as a marker of bone pathology and future bone damage.

The first description of BME occurring at the RA wrist appeared in the radiology literature from Koenig and colleagues [15]. It was initially thought to be rare [16], but in 1998 this was refuted by findings from a New Zealand (NZ) cohort of 42 patients with early RA [17], in which BME was scored in 64% of cases. Common sites were the lunate, triquetrum, and the capitate [17]. Peterfy and colleagues [18] recently reviewed MRI findings from four multicenter randomized controlled trials, including data from 522 patients with RA, and showed that BME (referred to as osteitis) was most frequently scored at the navicular (scaphoid), lunate, capitate, and radius at the wrist and the 2nd and 3rd metacarpals at the fingers and had a bone involvement pattern similar to that of erosions. Others have since confirmed that BME is common in early as well as late RA, and estimates of frequency range between 34% and 68% [17,19-21]. Ostendorf and colleagues [19] described BME at the hands in 9 of 25 patients with early RA (within 12 months of onset). The investigators also scanned 10 patients with very early disease at a median of 9 weeks from first symptoms and found that hand MRI scans were normal or showed tenosynovitis only but that MRI scans of the forefoot revealed BME at the metatarsophalangeal (MTP) joints in 70% of patients [19]. This recalls the radiographic finding that the first site for development of bone erosions is the 5th MTP joint [1] and suggests the possibility that BME in RA might be a pre-erosive lesion.

MRI bone edema – a biomarker for aggressive erosive disease

What is the prognostic significance of the BME lesion? This question was addressed by the NZ RA cohort study,

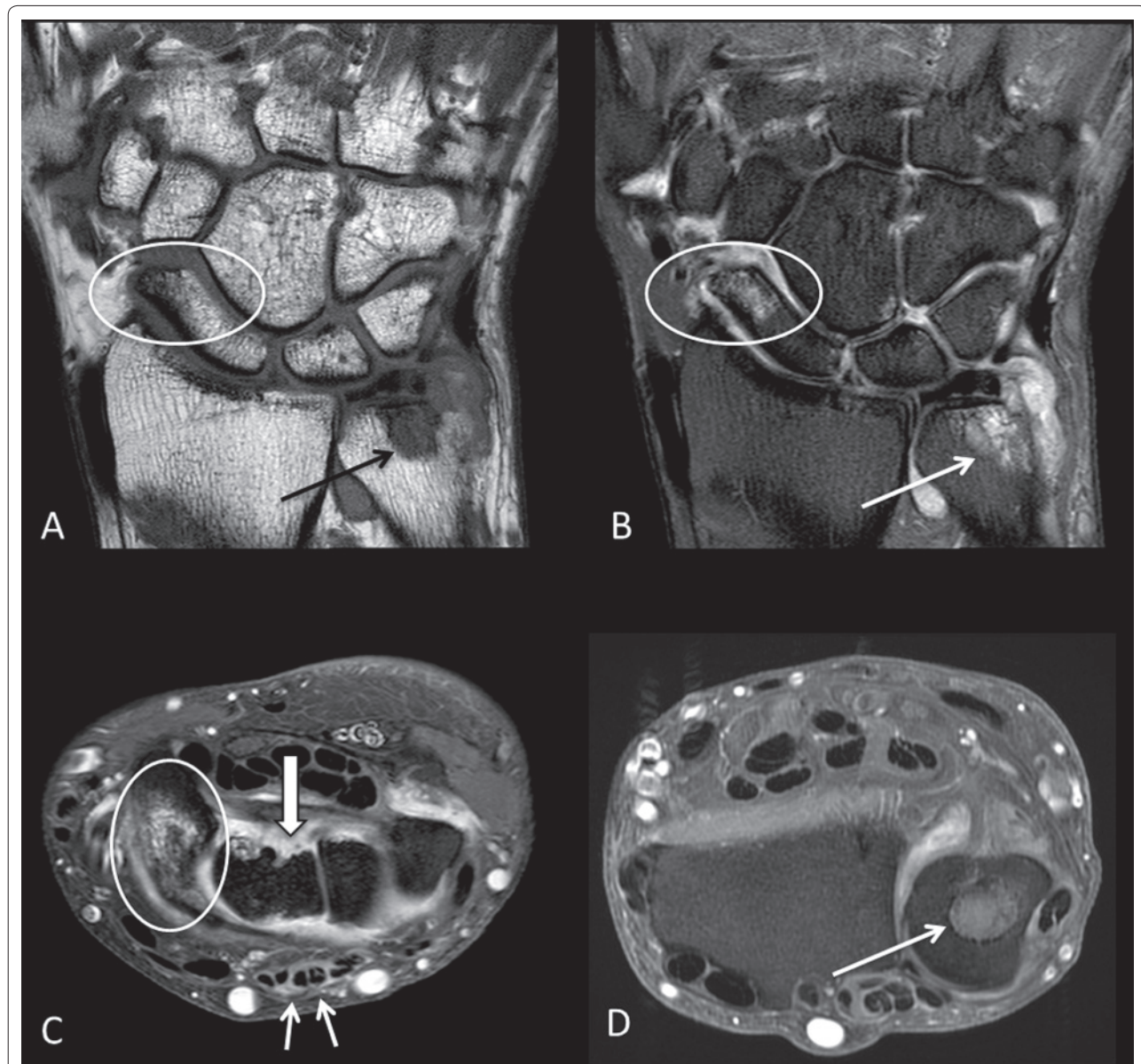


Figure 1. 3 Tesla magnetic resonance imaging (3T MRI) scans of the dominant wrist from a 61-year-old American Indian man with seropositive rheumatoid arthritis of 19 months' duration. (A) T1-weighted (T1w) coronal image of the wrist shows a region of bone marrow edema (BME) as low-signal within the pole of the scaphoid (circle). A circumscribed low-signal region in the distal ulna (arrow) is consistent with erosion, which is confirmed on adjacent slices. **(B)** BME within the scaphoid appears as a high-signal region on a T2-weighted spectral selection attenuated inversion recovery (SPAIR) coronal image, and BME is adjacent to the ulnar erosion (arrow). **(C)** Post-contrast T1w axial image confirms BME within the scaphoid. This and adjacent slices were used to score the BME as RAMRIS grade 2. Extensive synovitis within the joint, an erosion at the capitate (wide arrow), and low-grade tenosynovitis within the extensor tendon sheath (two short arrows) are shown. **(D)** Post-contrast T1w axial image shows erosion within the ulna containing weakly enhancing synovium. RAMRIS, rheumatoid arthritis magnetic resonance imaging score.

in which patients were followed 1, 2, 6, and 8 years after presentation [17,22-24] clinically, radiographically, and by using 1.5-T contrast-enhanced MRI scans at 0, 1, and 6 years. Individual carpal bones affected by BME at baseline were examined for the presence of new MRI erosions at 1 and 6 years, and a strong association was discovered. At 1 year, 542 paired observations (from

baseline and 1 year) were examined, and an odds ratio (OR) of 6.47 was derived for the likelihood that BME would be followed by MRI erosion [22]. After 6 years, paired observations were available at 407 sites in 31 patients [23,25]. An intriguingly similar OR of 6.5 predicted erosion from baseline BME [23]. Additionally, the sum score for BME at the wrist predicted both

components of the XR Sharp/van der Heijde score for joint damage [26], joint space narrowing (JSN) plus erosion, separately and together with an r^2 value of 0.2. This indicates that 20% of the variance of the XR data (reflecting damage at both hands and feet) was predicted by an MRI scan of one wrist taken 6 years earlier. Interestingly, initial MRI BME scores (at one wrist) also predicted overall physical function in these patients at 6 years [27] and even tendon function after 8 years (chi-squared 15.3, $P = 0.0005$) [24]. Taken together, the findings from this cohort were dramatic and suggested that MRI BME in early RA has a profound negative influence upon outcome, both within the bone (development of XR erosions), cartilage (JSN), and tendons and in terms of overall physical function. The logical conclusion is that something profoundly important is going on within the bone marrow in RA.

More recently, these findings have been replicated in larger RA cohorts from different centers [28-30]. Haavardsholm and colleagues [28] reported on 84 Norwegian patients with RA who were followed for 1 year and found that the only independent predictors of MRI and XR erosive progression were baseline MRI BME and male sex. Other factors such as the rheumatoid arthritis magnetic resonance imaging score (RAMRIS) [31] for synovitis, C-reactive protein (CRP), and anti-cyclic citrullinated peptide (anti-CCP) status did not achieve predictive significance. Hetland and colleagues reported on a separate Danish cohort at 2 years [29] and 5 years [30]. These patients were enrolled into the CIMESTR (Ciclosporin, Methotrexate, Steroid in RA) study, a double-blind, placebo-controlled trial in patients with early active RA that was treated aggressively with traditional disease-modifying anti-rheumatic drugs plus or minus cyclosporine [32]. In the 130 who had a baseline MRI scan of the hand, the RAMRIS bone edema score was the only independent predictor of erosive progression (change in total Sharp score = Δ -TSS) at the 2-year review and alone explained a very large percentage (41%) of the variance [29]. The P values were less than 0.001 for this association and 0.08 for anti-CCP status [29]. Very similar findings were reported at 5 years [30] when no difference was found between treatment groups on unblinding, and the predictive power of baseline MRI BME was confirmed (again $P < 0.001$) while the anti-CCP status just achieved significance ($P = 0.03$). It is interesting to note that the baseline BME score explained 23% of the variation in the progression of the TSS at 5 years; this figure is almost identical to that of the NZ cohort at 6 years [23]. Several other studies have confirmed the association between MRI BME and erosive progression [33-35], and these data are summarized in Table 1.

MRI BME has also been found to be a strong predictor of evolution from undifferentiated inflammatory arthritis

(UA) to RA by Danish and Japanese groups [36-38]. Duer-Jensen and colleagues [36] studied 116 patients with early UA and found that 23% developed definite RA over the course of 12 to 23 months. A prediction model was constructed from baseline factors. When this included MRI BME at the hand and wrist in combination with clinical hand arthritis, positivity for rheumatoid factor, and morning stiffness lasting more than 1 hour, the optimal model correctly identified outcome in 82% of the patients. An alternative model, which did not incorporate MRI BME, predicted RA with only 60% accuracy. BME was also an independent predictor of progression (not achieved by MRI synovitis score, anti-CCP status, or CRP). Tamai and colleagues [37,38] also studied this question and described similar findings. They used a 1.5-T MRI system (as opposed to the 0.6-T unit of the Danish group) and studied a cohort of 129 patients with UA [38]. The authors' prediction model contained, as explanatory variables, positivity for anti-CCP or IgM-RF or both, MRI-proven symmetric synovitis, and MRI BME or bone erosion or both. At 1-year follow-up, 71.3% of the patients who were positive for two of these variables at baseline had developed RA. However, of the 22 UA patients who were positive for both anti-CCP and MRI BME, all progressed to RA with a positive predictive value of 100% [38]. These results confirm the diagnostic power of bone marrow edema as a biomarker.

What is the link between MRI BME, synovitis, and erosion?

Most of the studies mentioned above have included measures of synovitis, which, according to the traditional paradigm of rheumatoid pathology, is the precursor to bone erosion. The association between synovitis and BME was explored by Conaghan and colleagues [39] at the metacarpophalangeal joints. They found that MRI synovitis (increased synovial thickness) was greater in joints with BME than without and that both lesions responded to intra-articular corticosteroid. More recently, this group analyzed MRI results from the GO-FORWARD (Golimumab for Subjects with Active RA Despite Methotrexate) study, which investigated efficacy of the anti-tumor necrosis factor (anti-TNF) agent golimumab [40] and found that the CRP decrease associated with a therapeutic response paralleled reductions in both synovitis and BME. Most cohort data have indicated that these measures correlate strongly with each other and that they often occur together within the same joint, but the crucial question remains: which is the pre-erosive lesion? Or could it be that both contribute to subsequent bone damage [6]?

Mundwiler and colleagues [21] attempted to tease this out further in their study of MRI scans of the 3rd, 4th, and 5th MTP joints in 50 patients with RA. The authors

Table 1. Chronological review of studies showing that magnetic resonance imaging bone marrow edema predicts erosive progression in rheumatoid arthritis

Study	Year	Description	Association with erosion progression	Outcome measure (XR, MRI, or CT)
McQueen <i>et al.</i> [22]	1999	In this NZ cohort, 42 patients with early RA were enrolled at presentation, within 6 months of symptom onset.	Baseline bone edema score predicted MRI erosion score at 1 year (OR = 6.47, $P < 0.001$).	MRI erosion score at dominant wrist
Savnik <i>et al.</i> [35]	2002	Danish cohort of 22 patients had RA for less than 3 years. Patients were followed at 1 year.	Presence of bone edema in wrist bones at baseline was the strongest individual predictor of bone erosions at 1 year ($P < 0.007$).	MRI erosions at dominant wrist
McQueen <i>et al.</i> [23]	2003	NZ cohort was reviewed at 6 years. Patients were treated with non-biologic DMARDs. MRI outcome data on 31 patients and XR outcome data on 34 patients are available.	Baseline bone edema score was only MRI feature on multivariate analysis to predict 6-year Sharp score ($R^2 = 0.20$, $P = 0.01$). At each bone, OR (95% CI) for bone edema predicting MRI erosion was 6.5 (2.78 to 18.1).	XR erosion score at hands and feet and MRI erosion score
Palosaari <i>et al.</i> [33]	2006	Twenty-seven patients with early RA had a disease duration of less than 12 months. Contrast-enhanced MRI data on 24 patients at 2 years are available.	Bone edema score was the only baseline variable to predict erosive progression at 2 years on multivariate regression (OR = 4.2, 95% CI = 1.3 to 13.8). At each bone, ORs (95% CIs) of predicted erosion at 1 and 2 years were 28 (11.7 to 67.1) and 14.9 (6.3 to 34.9), respectively.	MRI erosion score wrist
Haavardsholm <i>et al.</i> [28]	2008	Eighty-four patients with RA had a disease duration of less than 1 year. Follow-up was at 1 year. Traditional DMARD therapy (plus anti-TNFs in two patients by 1 year) was used.	Baseline MRI bone edema score of more than 2 RAMRIS units was an independent predictor of both XR (OR = 2.77, 95% CI = 1.06 to 7.21) and MRI erosive progression.	MRI erosive progression at dominant wrist and XR erosive progression at the hands
Hetland <i>et al.</i> [29]	2009	One hundred thirty patients with early RA had a disease duration of 3.3 years. Combination non-biologic DMARD therapy, including ciclosporin, or placebo was used. Two-year follow-up data are available.	Baseline bone edema score was the only independent predictor of 2-year change in Sharp score (multivariate linear regression): coefficient = 0.75 (95% CI = 0.55 to 0.94, $P = 0.001$).	XR erosion score at hands and feet
Mundwiler <i>et al.</i> [21]	2009	Forty-six patients had a disease duration of less than 5 years. MRI and XR of 3rd, 4th, and 5th MTP joints of both feet were performed. Patients were treated with traditional and biologic DMARDs; 1- and 2-year data are available.	Bone edema predicted MRI erosions at 6 and 12 months with PPVs of 0.25 and 0.50 and NPVs of 0.99 and 0.99, respectively. At each bone, ORs for bone edema being followed by erosion were 34.2 and 68.0 at 6 and 12 months, respectively.	MRI erosion score at 3rd, 4th, and 5th MTP joints bilaterally
Hetland <i>et al.</i> [30]	2010	In the same cohort as above (Hetland <i>et al.</i> [29]), 139 patients completed 5 years of follow-up. No treatment influence on erosion progression was noted. No biologics were used.	MRI bone edema was an independent predictor of XR progression (coefficient = 0.82, CI = 0.50 to 1.13, $P < 0.001$). Bone edema explained 23% of the variation in the progression of the TSS (Pearson's $r = 0.48$).	Change in XR erosion score at hands and feet (TSS progression rate)
Döhn <i>et al.</i> [57]	2011	Fifty-two patients with biologic-naïve RA and a disease duration of 7 years were followed for 12 months on anti-TNF therapy (adalimumab/methotrexate).	When baseline MRI bone edema was present versus not present, RR for erosive progression in the same bone on CT at 12 months was 3.8 (95% CI = 1.5 to 9.3, $P = 0.004$). If bone edema was 'ever present' versus 'never present', RR was 14.8 (95% CI = 4.3 to 50.7).	CT erosions at dominant wrist and 2nd to 5th MCP (site-by-site).
Bøyesen <i>et al.</i> [34]	2011	Eighty-four patients with RA (same cohort as that of Haavardsholm <i>et al.</i> [28])	Baseline total MRI bone edema score predicted MRI erosive progression at 1 year with an OR of 1.28 (95% CI = 1.01 to 1.64, $P = 0.04$).	MRI erosive progression

anti-TNF, anti-tumor necrosis factor; CI, confidence interval; CT, computed tomography; DMARD, disease modifying antirheumatic drug; MCP, metacarpophalangeal; MRI, magnetic resonance imaging; MTP, metatarsophalangeal; NPV, negative predictive value; NZ, New Zealand; OR, odds ratio; PPV, positive predictive value; RA, rheumatoid arthritis; RAMRIS, rheumatoid arthritis magnetic resonance imaging score; RR, relative risk; TSS, total Sharp score; XR, x-ray.

found that the absence of BME made the formation of an MRI erosion over the course of 1 year highly unlikely (negative predictive value at 12 months of 0.99) but that having BME dramatically increased the likelihood that an erosion would form. On baseline scans, BME was accompanied by synovitis in all but one case. However, synovitis was an isolated finding in 52 MTP joints at baseline, and only 6% of these developed subsequent bone defects or erosions. These results suggest that coexistent BME could be what gives synovitis its apparent association with later erosion. However, many of these patients began anti-TNF therapy during the study and this could have had an independent influence. In the NZ cohort referred to above, MRI synovitis was predictive of erosions at 1 year (with an OR of 2.14 compared with 6.4 for BME), but by the time the cohort was followed out to 6 years, this effect had disappeared (whereas the influence of BME remained). The data from this group are particularly important as they did not receive anti-TNF agents, which could confound the issue due to their powerful erosion-suppression effect. Therefore, the NZ data may have more closely followed the natural history of RA.

US data related to synovitis are interesting to review here because grayscale synovial thickening has been associated with later bone erosion in some 12-month prognostic studies [34,41], but the strongest association has been with time-integrated measures of synovial vascularity from power Doppler ultrasound (PDUS), as reported by both Naredo and colleagues [42] and Brown and colleagues [43]. Clearly, using US alone does not allow bone edema, which is invisible to the US probe, to be monitored, but it is interesting to speculate whether those joints with the most vascular synovium and thus highest US Doppler activity could be those with the most active underlying osteitis. A recent paper by Boesen and colleagues [44] addressed this question. They investigated correlations between RAMRIS scores for bone edema and synovitis and the PDUS score at the wrist joints in 50 patients with RA. The strongest correlation was between the RAMRIS bone edema and PDUS scores ($\rho = 0.6$, $P < 0.001$). BME was confirmed to be a vascular lesion by Hodgson and colleagues [45] by using dynamic-enhanced MRI. Interestingly, those authors found this measure of BME to be more sensitive than the static RAMRIS bone edema score, suggesting that low-grade osteitis may sometimes be below the level of detection of standard MRI imaging (as has also been indicated by comparative MRI/histology studies; see 'MRI BME in RA represents osteitis' section below [46]).

Cartilage damage occurs late and in parallel with erosion

How does cartilage damage fit into the equation? A recent study examined cartilage loss at rheumatoid wrist

joints by using MRI and compared this with a control group [47]. Unexpectedly, cartilage thinning was very minor in the group with early RA (<2 years) and not significantly different from that of controls, but there was active BME and quite extensive carpal erosion in many of these patients. If the sequence of pathology is from synovitis to cartilage damage to bone erosion, then one would expect cartilage thinning to be an early lesion. Instead, this evidence suggests that the rheumatoid erosion has a bone-centered origin and that cartilage damage occurs as a separate consequence, a conclusion that was also proposed by van der Heijde [48] in a review of radiographic progression of RA joint damage. The author noted (of JSN and erosion) that 'these two processes often occur in parallel but joints in which erosions are present show a preference for progression of erosions and ... (in) joints with JSN present, there is a preference for worsening of JSN over development of erosions'.

MRI BME in RA represents osteitis

Three studies have investigated the histology of RA BME. Regions of interest were identified on preoperative MRI scans from patients with RA about to have joint replacement surgery, and then samples of resected bone were examined by using histological and immunohistochemical techniques [46,49,50]. McQueen and colleagues [46] identified seven matched MRI/bone samples from four patients with informative preoperative scans and found an intense patchy lymphoplasmacytic infiltration within the subchondral marrow in a patient with high-grade MRI BME, whereas moderate osteitis occurred where BME was moderate and osteitis was very low-grade or absent in three samples without BME. This again suggested a floor effect for standard MRI in terms of imaging BME, below which mild osteitis could still be present [46]. Jimenez-Boj and colleagues [49] performed a similar study examining 12 joints from three patients and came to the same conclusion, that MRI BME represents osteitis, featuring a vascular lymphocytic infiltrate with replacement of marrow fat and sometimes an associated cortical break (erosion). A more detailed study was then performed by the NZ group, expanding the sample to a total of 28 bones from 11 patients [50]. Cells identified within regions of osteitis included plasma cells, B cells, T cells, and macrophages, and this inflammatory infiltrate replaced marrow fat adjacent to bony trabeculae, upon which large numbers of osteoclasts were identified within lacunae. Osteoclast numbers correlated with numbers of macrophages ($r = 0.54$, $P = 0.003$) and plasma cells ($r = 0.61$, $P = 0.005$). There was also a strong correlation with the receptor activator of nuclear factor kappa B (RANKL) score ($r = 0.59$, $P = 0.004$). B-cell aggregates were identified in some samples, which were

reminiscent of the ectopic lymphoid tissue that can be found in active rheumatoid synovium [51]. The conclusion from these findings was that the rheumatoid bone marrow is a site of active pathology with a histology similar to that found within synovial membrane but with the addition of osteoclasts closely apposed to trabecular bone and likely to be mediating the erosive process. Figures 2 and 3 illustrate this hypothesis diagrammatically.

Could MRI BME and periarticular osteopenia be linked?

If a region of trabecular bone contains a cellular infiltrate that replaces marrow fat, then on MRI T2w or STIR sequences, BME will appear as described above. If bony trabeculae are undamaged, there will not be osteopenia, because the XR can detect the calcium in bone only and does not image soft tissue within the marrow. However, if bony trabeculae are thinned (for example, by an osteoclast-mediated resorptive process), then the two conditions could occur together and become superimposed [52]. The histology of BME described by Dalbeth and colleagues [50] showed features consistent with this hypothesis as a marrow infiltrate of macrophages, lymphocytes, and plasma cells was found directly in contact with large numbers of osteoclasts sitting in resorption lacunae on bony trabeculae. Bøyesen and colleagues [34] investigated the link between radiographic and MRI bone changes in the Norwegian cohort of 84 patients mentioned above [28]. As stated above, BME was an independent predictor of MRI erosive progression, but when bone mineral density (BMD) loss at 3 months was examined, there was only a trend towards this being associated with erosion progression. However, BMD was measured by digital XR radiogrammetry by using the method described by Hoff and colleagues [53], which estimates cortical bone at the centers of metacarpals II, III, and IV, and not trabecular bone in the periarticular region, where bone marrow edema tends to occur. de Rooy and colleagues [54] investigated the related issue of whether low BMD predicted the development of RA in patients with UA. The authors confirmed that patients with reduced BMD at the hands were more likely to develop RA with an OR of 6.1. This recalls the work of Tamai and colleagues [38] cited above, which showed that MRI BME in patients with UA predicts the later development of RA. Clearly, more work examining the immediate periarticular region and comparing BMD and MRI BME at that site would be interesting.

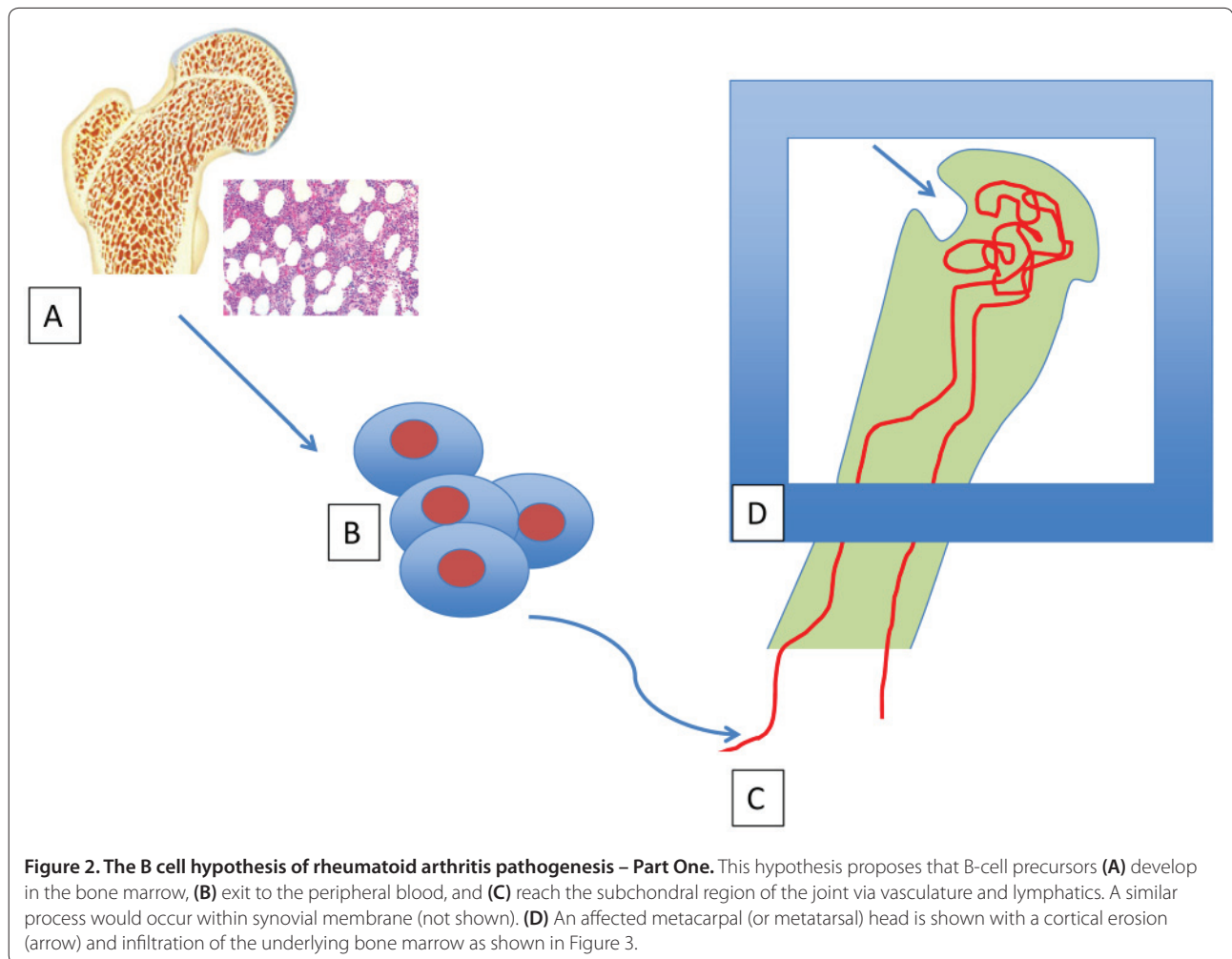
There are more data from quantitative histological studies of periarticular rheumatoid bone from the pre-MRI era. These revealed findings that were very similar to those described above [50], with regions of periarticular osteopenia featuring osteoclasts concentrated

on trabeculae and an increase in the active osteoid surface in RA compared with OA specimens (12% versus 4.8%, $P < 0.001$) [55]. This study and others were summarized by Goldring and Gravallesse [56] as revealing 'the presence in the marrow space of local aggregates of inflammatory cells, including macrophages and lymphocytes (with) ... an increase in resorption surfaces, which are often populated by osteoclasts'. The authors went on to remark that 'the absence of direct synovial interaction with the bone surfaces indicates that different cellular interactions are involved in the recruitment and activation of the bone resorbing cells' [56]. It seems possible that MRI BME and radiographic periarticular osteopenia reflect two different faces of the same entity: the rheumatoid bone lesion. XRs reveal the trabecular resorption taking place, whereas MRI reveals the inflammatory infiltrate within the marrow space.

The influence of biologics on MRI BME (osteitis)

1. Anti-TNF therapy

If the rheumatoid bone lesion that is revealed on MRI as BME and that is histologically osteitis is pathologically important, then it would be expected to respond to therapy, especially therapy that stops the progression of bone erosions. A number of studies of anti-TNF agents have examined the question of regression of MRI synovitis and BME [40,57]. Døhn and colleagues [57] examined 52 patients with erosive biologic-naïve RA by using MRI as well as other imaging during adalimumab/methotrexate combination therapy. As was the case for other non-biologic studies discussed already, baseline MRI BME predicted progression of computed tomography (CT) erosions with a relative risk of 3.8 (95% confidence interval of 1.5 to 9.3). At 12 months, MRI synovitis was registered in 95% of joints and BME in 20% of bones, but there was no significant change in MRI or US erosion scores, indicating that overall erosive progression was arrested. This effect was also apparent in the more recent MRI studies of golimumab therapy [40], in which both osteitis and synovitis persisted (but at reduced levels) despite virtual cessation of erosion. This throws a spanner in the works for both traditional and new hypotheses of erosion generation in RA, which assume synovitis or osteitis or both as the pre-erosive lesion. This has been referred to as the 'disconnect' and has been postulated to be due to a reduction in TNF-mediated RANKL signaling to osteoclasts, without which they are inactive and do not resorb bone [58]. There is evidence for this from animal models; for example, a fusion protein of osteoprotegerin which inhibits RANK-RANKL interactions can prevent bone erosion in TNF-transgenic mice [59]. Similarly, a study of denusomab, a RANKL-blocking monoclonal, revealed no significant clinical improvement in treated RA patients despite

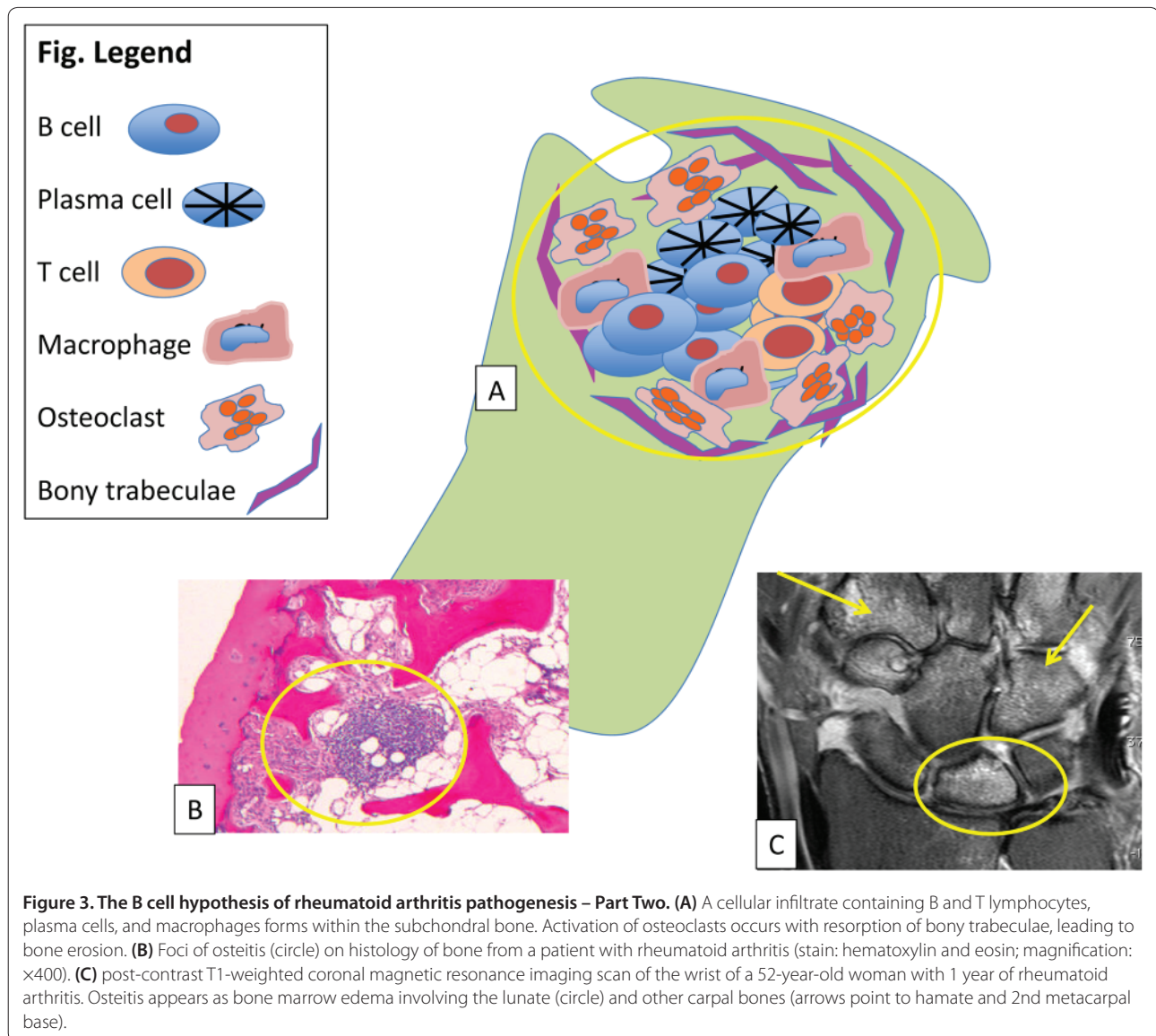


marked suppression of bone erosion on MRI and XR [60]. Interestingly, radiographic JSN continued to progress in these patients despite the suppression of erosion, suggesting that a different mechanism may mediate this form of joint damage, as also proposed by van der Heijde and colleagues [48].

2. B-cell depletion

What happens to osteitis after treatment with B cell-depleting therapy, which is also known to halt the progression of XR erosions? This question was partly answered by the abstract that Peterfy and colleagues [61] submitted last year to the European League Against Rheumatism, in which MRI wrist scans from 185 patients in the Study of MabThera [Rituximab] in Patients with Rheumatoid Arthritis and Inadequate Response to Methotrexate (RA-SCORE) study were examined. These patients with RA were biologic-naïve and had responded inadequately to methotrexate. They were treated with rituximab/methotrexate or placebo/methotrexate, and

MRI outcomes were assessed. A marked and significant reduction in osteitis (BME) was observed in rituximab-treated groups from weeks 12 to 24, and there was also a reduction in MRI synovitis scores. Consistent with earlier studies using XR erosions as an endpoint [62], there was also virtual cessation of erosion progression and JSN. The finding that depletion of B cells markedly reduced osteitis implies that the bone marrow B cell (or its offspring, the plasma cell) is likely to be intimately involved in the process of erosion. Could RANKL again be implicated in this scenario? Very recently, Boumans and colleagues [63] explored this by using synovial biopsy specimens to evaluate RANKL expression in osteoclast precursors present within the synovium. Sixteen weeks after rituximab/methotrexate treatment, they found a 99% decrease in RANKL-positive osteoclast precursors ($P = 0.02$) and a 37% decrease in RANKL expression in the synovium. Presumably, a very similar process could be taking place in the subchondral bone marrow, but that tissue is much more difficult to obtain.



3. Interleukin-6R inhibition and T-cell costimulation blockade

In a study investigating the efficacy of interleukin-6R inhibition in 31 patients with RA, RAMRIS osteitis (BME) scores fell markedly among patients on tocilizumab, both as monotherapy and combined with methotrexate [64]. The authors noted that using MRI osteitis as an outcome measure allowed a therapeutic effect to be detected at 12 weeks, much earlier than the point at which radiographic abnormalities would have become apparent. Another study took things one step further by investigating patients with pre-RA (patients with UA who were anti-CCP-positive with synovitis at two joints). MRI synovitis, osteitis, and erosion were monitored during treatment with abatacept or placebo [65]. At 6 months, osteitis scores in the group had improved almost 70%

from baseline, but in those receiving placebo, the mean score increased by 41%. Thus, the finding that osteitis is an important pre-erosive lesion has now been adopted by pharmaceutical companies and is being employed to show efficacy of biologic therapies much earlier than was previously possible. This should translate to a more rapid assessment of response and overall improved patient management.

Conclusions

In summary, over the last 15 years, studies investigating MRI BME have provided new insight into the pathogenesis of RA. There is firm evidence from many groups that BME is the strongest of many conventional and imaging biomarkers for prediction of erosive progression. It is also a predictor of an aggressive RA phenotype

associated with functional decline and the transition from UA to RA. Histologically, in late disease, BME has been shown to be osteitis, comprising a lymphoplasmacytic inflammatory infiltrate within the marrow, directly adjacent to osteoclasts sitting in lacunae on trabecular bone. Resorption of bony trabeculae is likely to result in the radiographic sign of periarticular osteopenia, and marrow infiltration by osteitis with resultant osteoclast activation could be driving this process. MRI studies of the therapeutic response to biologics have shown osteitis to be responsive to therapy with anti-TNF, B cell depleting therapy, and other biologic agents. Thus, a whole new dimension of rheumatoid pathology now needs consideration, and the bone marrow compartment is at center stage.

This article is part of the series on *Is rheumatoid arthritis a bone marrow disease?* Other articles in this series can be found at <http://arthritis-research.com/series/marrow>

Abbreviations

anti-CCP, anti-cyclic citrullinated peptide; anti-TNF, anti-tumor necrosis factor; BMD, bone mineral density; BME, bone marrow edema; CRP, C-reactive protein; JSN, joint space narrowing; MRI, magnetic resonance imaging; MTP, metatarsophalangeal; NZ, New Zealand; OR, odds ratio; PDUS, power Doppler ultrasound; RA, rheumatoid arthritis; RAMRIS, rheumatoid arthritis magnetic resonance imaging score; STIR, short tau inversion recovery; T2FS, T2-weighted fat-saturated; T2w, T2-weighted; TSS, total Sharp score; UA, undifferentiated arthritis; US, ultrasound; XR, x-ray.

Competing interests

The author declares that she has no competing interests.

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