Bone pathology

A vital clue to deciphering bone pathology: MRI bone oedema in rheumatoid arthritis and osteoarthritis

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Evidence is mounting that MRI bone oedema is an important finding both in rheumatoid arthritis (RA) and osteoarthritis (OA). It is associated with pain in both conditions,1,2 signalling disease activity, and is also a marker of poor prognosis, predicting joint damage and radiographic progression.3,4 While the articular pathology of RA clearly differs from that of OA, the finding of bone oedema informs us about a region of critical importance to both conditions, the subchondral bone. This vital tissue, lying directly below the articular cartilage, has hitherto been inaccessible and consequently rather neglected. Using the window provided by MRI, the subchondral bone has now been shown to be far from an inert framework sitting passively beneath the joint, but rather to be intimately involved in the pathological processes producing joint inflammation and leading to destruction. This review will begin by describing the MRI characteristics of bone oedema and then explore data from clinical and histopathological studies that shed light on its nature and significance in RA and OA.

MRI BONE OEDEMA IN RA

Clinical studies

MRI bone oedema was first reported in RA at the wrist by Koenig et al in 1986.5 It has been described as having a diffuse “feathery” appearance with indistinct margins and is often associated with joint erosions.6 It was first recognised as a common lesion in early RA when described in 64% of a cohort of patients from New Zealand who had wrist MRI scans at the time of diagnosis.1 Others have since confirmed its frequency in early disease, including Ostendorf et al who described bone oedema at the forearm in 7 of 10 patients with normal hand MRI scans, who had only had symptoms for a median of 9 weeks.4 McQueen et al examined 15 sites at the wrist in 42 RA patients and used 542 paired observations at 1 year and 407 at 6 years to examine the fate of wrist bones that were not eroded at baseline.8 The risk of erosion was increased more than sixfold if bone oedema had been detected at that site previously. After 6 years, the bone oedema score at the wrist was the only single baseline MRI variable for the group as a whole to predict the Sharp van der Heijde score9 quantifying radiographic damage at both hands and feet. Analysis of these data showed that bone oedema was separately predictive of both the joint space narrowing and erosion components of this score, suggesting an influence not only on subchondral bone but also possibly on cartilage.10 In this cohort, baseline bone oedema was also, surprisingly, a predictor of function at 6 years as measured by the SF-36 and was the only separate clinical or MRI feature to achieve this.11

Recently, these findings have been confirmed by the largest MRI study of early RA reported to date. Haavardsholm et al followed 84 Norwegian patients over 1 year and found bone oedema and male sex to be the only baseline variables capable of predicting radiographic erosive progression.12 Groups from Denmark and Finland have also reported this association with erosion after 1 and 2 years.13–15 and recently a Japanese group showed in 80 RA patients that bone oedema was twice as common in those who were anti-CCP+ve, suggesting a link to an “aggressive disease” profile.16 Moreover, bone oedema scores have consistently been found to correlate with indicators of disease activity including CRP, ESR and pain score.17,18 High-grade bone oedema has been shown to occur frequently in regions targeted for joint replacement surgery, possibly because of its association with pain and bone destruction.17 Scores fall in response to anti-TNF therapy,19,20 and bone oedema was recently proposed to be part of the “inflammatory lesion” within the rheumatoid joint, which can be measured using a composite MRI score for bone oedema, synovitis and tenosynovitis.20 Consistent with this concept, Hodgson et al have now reported findings

**Abbreviations**: BMD, bone mineral density; BML, bone-marrow lesions; DMARD, disease-modifying antirheumatic drug; OA, osteoarthritis; RA, rheumatoid arthritis

![Figure 1](A) T1w postcontrast coronal MRI wrist scan of a patient with RA (6-year duration) showing extensive bone oedema involving the distal radius. (B) Matching multidetector CT scan reveals areas of erosion but no bone oedema.
from an MRI study of 25 RA patients where standard T2w sequences and dynamic enhanced scans of the MCPs and wrists were obtained pre- and post anti-TNF therapy.22 The relative enhancement rate on dynamic scans, which depends on tissue vascularity, was high in regions of bone oedema and fell after anti-TNF therapy, in very much the same way as has been observed in the inflamed synovium.22

Thus, bone oedema seems to play a crucial role in RA, straddling the processes of acute disease activity, where it is linked to inflammation and can respond to biological disease-modifying antirheumatic drugs, and structural joint damage, where the evidence is strong that it is a forerunner of radiographic progression and poor outcome. Clearly, there is an urgent need for it to be properly characterised histologically, but to achieve this, the hurdle of obtaining tissue has had to be overcome. Short of plunging a bone-marrow trephine needle into the wrist (which may not be well received), the subchondral bone in patients with early RA remains largely inaccessible. However, material is available from patients undergoing joint replacement, albeit with the caveat that this will represent advanced disease with a component of secondary osteoarthritis likely.

Histopathology and animal models
In April of this year, Jimenez-Boj et al described a study of 12 joints resected from three patients with advanced RA undergoing joint replacement. MRI scans were obtained preoperatively and attempts were made to align slices with histological sections of the excised bone.23 They found that regions of MRI bone oedema corresponded with regions of inflammation, being associated variously with invading pannus, lymphocytic aggregates and increased vascularity. McQueen et al recently published a similar study where bone was obtained from joints of the hands or feet of patients with longstanding RA.24 They also described florid bone oedema corresponding with active osteitis and compared this with regions where there was no bone oedema and no histological evidence of inflammation. These studies are exciting as characterisation of the cells involved may be informative as to the underlying immunopathology of RA. Lymphoid aggregates in close association with osteoclasts have been described by others in rheumatoid subchondral bone.25 and combined with imaging evidence, this suggests a mechanism for the genesis and progression of erosions.26 Data from animal models are also just emerging, and Proulx et al recently described an active inflammatory infiltrate replacing marrow fat, which corresponded with regions of MRI bone oedema, in a TNF-transgenic mouse model.27 Neither MRI bone oedema nor histological evidence of osteitis was found in wild-type mice without arthritis. Further studies of this type should allow bone oedema to be investigated in the early phases of arthritis, when human tissue is not usually available.

MRI BONE ODEMA IN OA
Clinical studies
Given that MRI bone oedema seems to represent such an important lesion in RA, it is slightly disconcerting to discover that it also occurs, possibly even more commonly, in OA where it is also linked to pain and radiographic progression. Most studies have focused on the knee and what are sometimes described as “hemispheric” regions of bone oedema28 that have been termed bone-marrow lesions (BML) in recognition of the lack of information about their histology. Felson et al investigated 401 patients with radiographic knee OA, and found BML in 78% of those with knee pain compared with 30% of those without, giving an odds ratio of 3.3 for the association. The same authors recently published a longitudinal case-control study over 15 months. This time, subjects were enrolled who did not have knee pain but had existing OA or were at high risk for developing this.29 Enlargement of the BML was the end point investigated and was much more common in cases knees (where pain developed) than controls with an odds ratio of 3.2.[1.5–6.8] Thus, the evidence is now strong that bone oedema is associated with pain in the setting of knee OA and that there is a dose–effect relationship in that more pain tends to go with larger lesions.

The BMLs of OA are also associated with progressive joint damage. Felson et al demonstrated a strong association between the presence of a BML and ipsilateral radiographic progression during follow-up at 15 and 30 months.30 Within the medial knee compartment, this risk was increased more than sixfold in those with medial BMLs. There was also an association between BMLs and malalignment, with for example a high prevalence of lateral lesions in valgus limbs.31 These authors concluded that “bone trauma” was the best explanation for the MRI bone oedema lesion with damage and deformity of subchondral bone eventually leading to radiographic change. An association between bone oedema and collagen breakdown products supports this.32 Levels of urinary C-terminal crosslinking telopeptide of type II collagen (CTX-II) reflecting collagen degradation were strongly associated with bone-marrow abnormality scores in a cohort of 377 patients. When followed longitudinally, changes in CTX-II correlated with changes in the BML score, indicating that both measures can be viewed as useful biomarkers in this disease.33 A further clue as to the nature of BMLs in OA comes from Lo et al, who investigated their association with bone mineral density (BMD) at medial and lateral compartments of the knee. They found that medial BMLs tended to occur in knees with higher relative medial tibial bone density, suggesting that local BMD reflects loading and also tying in with evidence from histopathology (see below) that bone oedema in OA is associated with trabecular remodelling and thickening.34

Histopathology and animal models
The studies correlating bone oedema with histopathology in OA have produced mixed results. Lesions described range from bone-marrow necrosis to fibrosis with vascularisation extending into the hyaline cartilage.35 36 However, a common feature is the replacement of bone-marrow fat with cellular or necrotic tissue which will be sufficient to produce increased signal on T2wFS or STIR MR images. In contrast to the situation in RA, there seems to be more fibrosis than inflammation, and a consistent feature has been thickening and remodelling of trabeculae along with subchondral cyst formation. Tan et al recently described bone oedema in OA finger joints, occurring at enthesal sites such as the insertions of collateral ligaments.37 Clearly, various processes are at play in the OA knee, depending on the site examined as well as disease severity and duration. There is some corroborating evidence from animal models of OA. Lahm et al, evaluated subchondral bone in dogs following an induced fracture.38 After 6 months, histomorphometry confirmed that trabecular bone volume was increased in the affected knee, indicating that remodelling had occurred. Another group compared MRI bone oedema with histology of the proximal tibia using the Pond–Nuki canine model.39 In these dogs, BMLs corresponded with regions of haematopoietic transformation within the bone marrow associated with inter trabecular fibrosis. However, haematopoiesis at this site is a feature of this particular model and does not occur in man, so animal data cannot always be extrapolated to human disease.

SUMMARY
In summary, MRI bone oedema is an important finding in RA and OA. Points of similarity and difference are listed in table 1. In RA, evidence from the imaging modality itself (increased signal
postcontrast indicating vascularity) and from limited histopathological studies suggests that bone oedema represents an inflammatory cellular infiltrate within the subchondral bone. It certainly behaves as such in response to biological disease-modifying antirheumatic drugs and could be more sensitive than synovitis as a marker of therapeutic response. It also predicts radiographic erosive progression and could be regarded as the “missing link” between joint inflammation and damage. In OA, bone oedema is similar in being strongly associated with pain but different in that it is probably not primarily an inflammatory lesion. The pain of OA bone oedema could be due to stimulation of the richly innervated periosteum by mediators released from necrotic tissue, to trabecular microfractures or to a pressure effect from abnormal tissue invading regions that should contain fat alone, as occurs in lucaemic infiltration. Histological studies have revealed fibrosis and trabecular thickening, to the point that bone density can be increased. This would fit with a process of bone remodelling and fibrosis leading on to joint damage with radiographic progression. Clearly, the subchondral bone is not “inert” in OA any more than it is in RA, and while bone oedema may be a different lesion histologically in these conditions, it is a red flag in both for progressive bone damage and potentially an important biomarker for use in clinical trials.

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