OsteoArthritis and Cartilage (2006) **14,** 1081–1085

doi:10.1016/j.joca.2006.05.011

Osteoarthritis and Cartilage

International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

MRI of bone marrow edema-like signal in the pathogenesis of subchondral cysts

J. A. Carrino M.D., M.P.H.†*, J. Blum M.D.‡, J. A. Parellada M.D.§, M. E. Schweitzer M.D.‖ and W. B. Morrison M.D.‡

† *Harvard Medical School, Department of Radiology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA*

‡ *Department of Radiology, Thomas Jefferson University Hospital, Philadelphia, PA, USA*

§ *Department of Radiology, DII – Diagnostic Imaging, Inc., Frankford Hospitals – Torresdale Campus, Philadelphia, PA, USA*

‖ *Department of Radiology, New York University, Hospital for Joint Diseases, New York, NY, USA*

Summary

Objective: To determine if a relationship exists between bone marrow edema-like signal and subchondral cysts on magnetic resonance imaging (MRI).

Design: Retrospective cohort of 32 patients with two sequential knee MRI. Patients with acute trauma, infection, neoplasm, or osteonecrosis were excluded. The degree of osteoarthritis was assessed using an adaptation of the Baltimore Longitudinal Study of Aging (BLSA) scale. Initial and follow-up exams were reviewed for presence, location, size and changes of marrow edema-like signal, subarticular cysts and cartilage abnormality. All locations in the knee were aggregated for analysis with descriptive statistics.

Results: The mean time interval between exams was 17.52 months (range 2.1–40.1 months). There were 23 cysts: 11 (47.8%) new, 6 (26.1%) increased size, 1 (4.4%) decreased size, and 5 (21.7%) no change in pre-existing lesions. Cysts always arose from regions of marrow edema-like signal. There were 68 subarticular areas of marrow edema-like signal: 16 (23.5%) new, 23 (33.8%) increased size, 17 (25%) decreased size, 11 (16.2%) resolved and 1 (1.5%) no change in pre-existing lesion. Marrow edema-like signal size always changed with cyst development: increased in 6/11 (54.5%), decreased in 2/11 (18.1%) and resolved in 3/11 (27.2%). Change in cyst size was always accompanied by a change in edema-like signal size. An MRI visible cartilage abnormality was adjacent to 87% (20/23) of cysts. The mean BLSA score changed from 2.6 to 3.6 indicating an overall progression of osteoarthritis.

Conclusion: Subchondral cysts develop in pre-existing regions of subchondral bone marrow edema-like signal.

Key words: Magnetic resonance imaging (MRI), Osteoarthritis, Bone marrow, Subchondral cyst.

Introduction

Osteoarthritis is a heterogeneous group of conditions that lead to joint symptoms and signs that are associated with defective integrity of articular cartilage with related changes in the underlying bone and at the joint margins[1]. Osteoarthritis of the knee is a multifactorial process that has been estimated to affect up to 15% of the United States population 65 years of age and older[2] and it is estimated that 12% of 25–75 year olds have symptoms and signs of osteoarthritis. Noninvasive evaluation of the knee joint has become particularly important with the interest in developing new treatment methods for articular cartilage abnormalities. Cartilage thinning, focal defects, meniscal lesions, ligamentous abnormalities and bone marrow edema-like patterns are frequently demonstrated on magnetic resonance (MR) images in patients with advanced osteoarthritis[3]. Osteoarthritis associated bone marrow edema-like signal lesions are an expression of a number of noncharacteristic histologic abnormalities that include bone marrow necrosis, bone marrow fibrosis, and trabeculae abnormalities[4]. Moreover, subchondral cystic lesions appear as well-defined areas of fluid signal on magnetic resonance imaging (MRI) corresponding to well-defined areas of lucency with sclerotic margins on radiography. Subchondral cysts are known to be associated with osteoarthritis[5]. Anecdotally, we have observed a relationship between these two imaging manifestations of osteoarthritis. However, no data are available on changes in subchondral bone (cysts, bone marrow edema, sclerosis) over time in knee osteoarthritis. The purpose of this study was to determine if a temporal relationship exists between bone marrow edema-like signal and the development of subchondral cysts.

Materials and methods

This study was approved by the institutional internal review board (IRB) as a medical records review and therefore

*Address correspondence and reprint requests to: John A. Carrino, M.D., M.P.H., Harvard Medical School, Department of Radiology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA. Tel: 1-617-732-7537; Fax: 1-617-278-6976; E-mail: jcarrino@partners.org

Received 30 October 2005; revision accepted 13 May 2006.

informed consent was not obtained from the research subjects. A retrospective cohort was selected based on a radiology information system search. Inclusion criteria were adult patients (greater than 18 years old) with two sequential MRI procedures of the same knee between the dates of January 1997 and December 2001. The imaging studies were requested as part of the providers' routine practice. The report text was searched for keywords ''geode'', ''cyst'', ''edema'', ''contusion'' or ''bruise''. Exclusion criteria were acute trauma, infection, inflammatory arthropathy (e.g., rheumatoid arthritis), neoplasm, osteonecrosis or use of a non-standard MRI protocol. The derived cohort consisted of 32 subjects, 20 women and 12 men with an age range of 29−80 years old (mean 51 years) after the application of inclusion and exclusion criteria from a total of 634 patients in the sample population. These were patients who had chronic or recurrent symptomatology. The indications given for the second MRI requested were 38% (12/32) pain, 28% (9/32) rule-out/meniscal tear, 22% (7/32) rule-out/internal derangement, and 13% (4/32) rule-out/osteoarthritis.

MRI was performed with a 1.5-T magnet (Signa 5x or LX, General Electric Medical Systems, Milwaukee, Wisconsin, USA) using a commercially available transmit-receive extremity coil. The routine clinical protocol incorporated the following sequences: sagittal spin-echo intermediate-weighted (repetition time (TR) range/echo time (TE), 1000−1200/20; 4-mm section thickness; 1-mm interslice gap; 256 × 192 matrix; 14-cm field of view; and 1 signal acquired), sagittal, coronal and axial fast spin-echo T2-weighted with fat saturation (TR range/TE range, 2400−6000/60−75; echo-train length of 8; 4-mm section thickness; 1-mm interslice gap; 256 × 192 matrix; 14-cm field of view; and 2 signals averaged), and coronal fast spin-echo intermediate-weighted (2000−3800/35−45, echo-train length of 8, 4-mm section thickness, 1-mm interslice gap, 256 × 192 matrix, 14-cm field of view, and 2 signals averaged). All fat suppression was performed using frequency selective chemical saturation (chemsat, General Electric Medical Systems).

The MR images were retrospectively evaluated and graded by simultaneous consensus of two experienced musculoskeletal radiologists using a structured reporting form. The radiologists were masked to patient identification, clinical symptoms of patients, time of scan acquisition (i.e., first or second scan), and results of initial scan when looking at follow-up scan. Subchondral cyst, bone marrow edema-like signal, cartilage abnormalities and overall osteoarthritis severity were initially independently assessed on the baseline and follow-up MRI examinations. Subsequently a side-by-side comparison was performed for verification. For evaluation of marrow edema-like signal, subchondral cysts and cartilage abnormalities six articular surfaces were assessed: patella, trochlea, medial femoral condyle, medial tibial plateau, lateral femoral condyle, and lateral tibial plateau. Osteoarthritis severity for the knee joint was assessed using an adaptation of the Baltimore Longitudinal Study of Aging (BLSA) scale[6]. This scale is used for radiographic scoring and we adapted it for MRI as follows. Numerical scores were assigned based on imaging findings for the femorotibial compartments as follows: presence of osteophytes (0 = none, 1 = small definite osteophyte(s), 2 = moderate osteophyte(s), 3 = large osteophyte(s)); narrowing/cartilage loss (0 = no narrowing, 1 = minimal but definite narrowing, 2 = moderate narrowing, 3 = severe narrowing or ''bone on bone''); sclerosis (0 = no sclerosis, 1 = definite subchondral sclerosis); osteophytes of tibial spines (0 = normal, 1 = sharpened spines). The values were summed for an overall score for each knee joint MRI examination.

Marrow edema-like signal was defined as a regional area of T2 prolongation (hyperintensity) near fluid signal with ill-defined or irregular margins. Volumes were calculated based on measurements in three dimensions using the square prism formula (volume = anteroposterior dimension × transverse dimension × craniocaudal dimension). A cystic lesion was defined as a subchondral well-defined well-marginated rounded fluid signal intensity (signal equal to joint cavity fluid) region. Volumes were calculated based on measurements in three dimensions using the prolate ellipsoid formula (volume = 0.5 × anteroposterior dimension × transverse dimension × craniocaudal dimension). Articular cartilage abnormalities were categorized as follows: normal signal and thickness, cartilage T2 signal alteration without thinning or defect, partial thickness thinning (diffuse articular area not exposing bone), full-thickness thinning (diffuse articular area exposing bone), partial thickness defect (focal measurable defect not exposing bone), and full-thickness defect (focal measurable defect exposing bone).

STATISTICAL ANALYSIS

Descriptive statistics were performed. Comparison was made between the baseline examination assessment and the subsequent follow-up examination assessments. The unit of analysis was per lesion: bone marrow edema-like signal and subchondral cyst. Each lesion was classified by the following categories of change. For *de novo* interval development of lesions the category of change was *new*. For pre-existing lesions the categories of change were *worsening* (*increased size*), *improvement* (*decreased size*), *complete resolution* and *no change*. Lesions were matched for articular location. Statistics were performed using computer software, StatCrunch version 4.0 (www.StatCrunch.com).

Results

The subject characteristics were mean age of 51 years (range 29-80 years) with 62.5% (20/32) females and 37.5%(12/32) males. The mean time interval between MRI exams was 17.52 months (1.46 years) with a range of 2.1−40.1 months. On initial MRI examination seven subjects had no evidence of osteoarthritis (BLSA score = 0), while 25 patients had at least evidence of osteophytosis with an initial mean BLSA score of 2.6 for the cohort. The cohorts' mean BLSA score increased to 3.6 indicating an overall progression of osteoarthritis. On the follow-up MRI examination, 21 subjects showed progression, while 11 had no interval change. There were a total of 69 lesions (bone marrow edema-like signal or subchondral cyst) identified on either the initial or follow-up MRI. The locations of the lesions were 26% (18/69) medial femoral condyle, 26% (18/69) medial tibial plateau, 17% (12/69) patella, 13% (9/60) trochlea, 9% (6/69) lateral femoral condyle and 9% (6/69) lateral tibial plateau.

There were 12 pre-existing subchondral cysts with the interval development of 11 lesions for a total of 23 subchondral cysts on the follow-up MRIs. For pre-existing lesions the following changes occurred: 6 increased size (*worsening*), 1 decreased size (*improvement*), 0 *complete resolution* and 5 *no change.* Almost all subchondral cysts, 92% (11/12), developed in a region of bone marrow edema-like

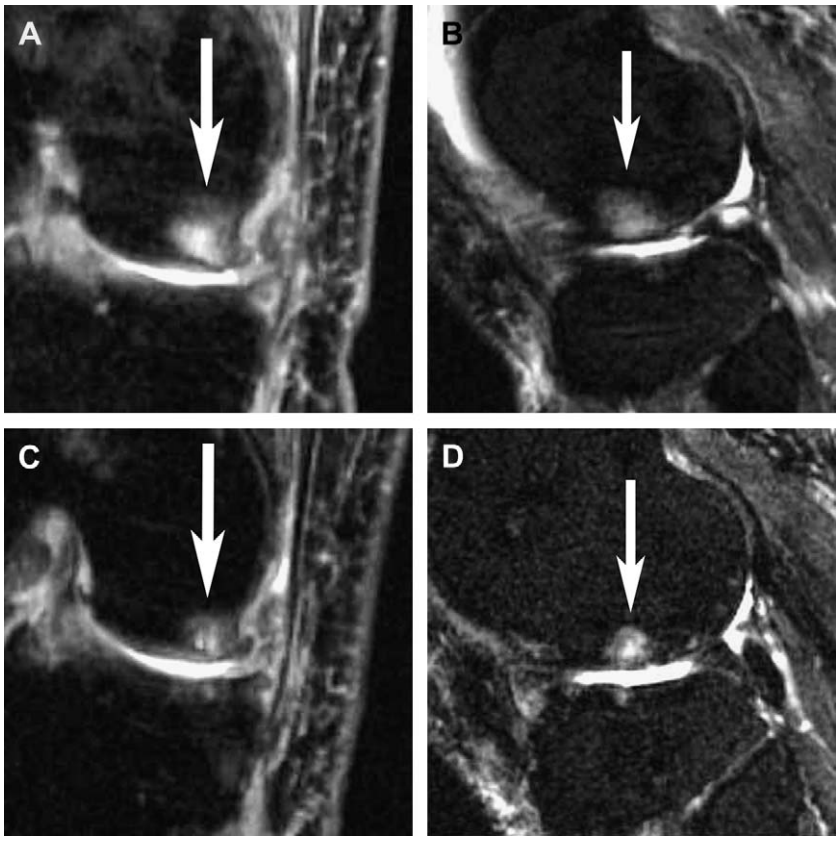

Fig. 1. Fifty-three-year-old male with subchondral cyst development. Baseline MRI: T2-weighted coronal (A) and sagittal (B) images show a subchondral region of bone marrow edema-like signal in the central portion of the lateral femoral condyle (arrows). Follow-up MRI 12.5 months later: T2-weighted coronal (C) and sagittal (D) images now show a subchondral region of well-circumscribed high signal intensity in the central portion of the lateral femoral condyle arising in the pre-existing bone marrow edema-like signal lesion (arrows). Note that the lateral meniscus body is absent reflecting a displaced tear.

signal (Fig. 1), which frequently had a "flame-shaped" configuration (Fig. 2). The baselines mean volume was 0.41 cm^3 (range 0.02–2.7 cm^3). The follow-ups mean volume was 0.35 cm^3 (range 0.01–3.5 cm^3). The mean volume of cysts decreased on the follow-up examinations due to the interval development of new smaller cysts offsetting the six pre-existing lesions that showed interval increase in size.

There were 68 subchondral areas of bone marrow edema-like signal on either the baseline ($n = 52$) or follow-up ($n = 57$) MRI. The baselines mean volume was 1.3 cm^3 (range 0.06–9.9 cm^3). The follow-ups mean volume was 1.4 cm^3 (range 0.06–12.5 cm^3). On the follow-up MRIs, there was interval development of 16 *de novo* lesions. For pre-existing lesions the following changes occurred: 23 increased size (*worsening*), 17 decreased size (*improvement*), 11 *complete resolution*, and 1 *no change*. Bone marrow edema-like signal size tended to fluctuate between baselines and follow-up MRI, whether a subchondral cyst formed or not and also changed irrespective of any change in pre-existing subchondral cysts status or size.

Cartilage lesions (any grade) were commonly seen overlying subchondral cysts and subchondral bone marrow edema-like signal on baseline and follow-up scans. Overall, 87% (20/23) of subchondral cysts were subjacent to an MRI visible cartilage abnormality (any grade). For baseline subchondral cysts there were 91% (10/11) cartilage lesions. For interval developed subchondral cysts, the follow-up images showed 83% (10/12) cartilage lesions. Subchondral bone marrow edema-like signal lesions were also seen with a high frequency subjacent to an MRI visible cartilage abnormality (any grade). For baseline scans with subchondral bone marrow edema-like signal lesions there were 92% (48/52) cartilage lesions. For follow-up scans with subchondral bone marrow edema-like signal lesions, there were 98% (56/57) cartilage lesions. Cartilage lesions were also seen without subchondral bone marrow edema-like signal lesions and cysts: five on the initial scans and six on the baseline scans.

Discussion

The imaging hallmarks of osteoarthritis are well known and described particularly in the knee: joint space narrowing (most often reflecting articular cartilage loss but in the knee could reflect meniscal extrusion), marginal osteophytosis and subchondral bone reaction. The type of subchondral bone reaction identified depends on the imaging modality. The radiographic manifestation of this reaction is subchondral sclerosis and well-defined rounded areas of lucency with sclerotic margins (subchondral cysts). In addition, MRI provides evaluation of the subchondral marrow often showing edema-like signal. There have been several reports relating subchondral marrow edema patterns to osteoarthritis[3,4,7–9] but none has examined the

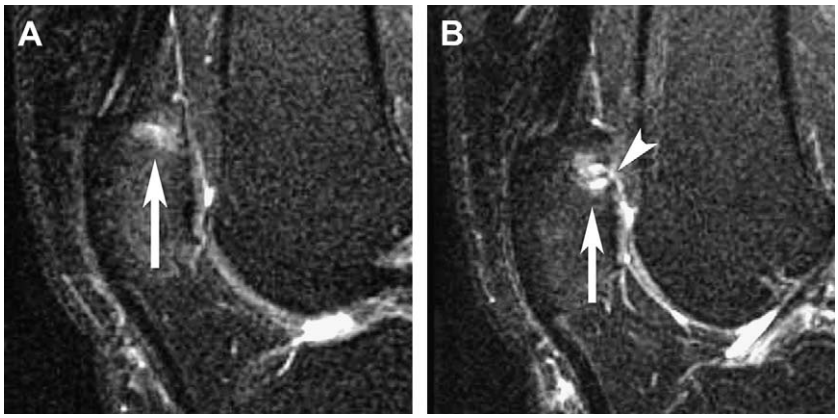

Fig. 2. Thirty-eight-year-old female with subchondral cyst development. Baseline MRI: T2-weighted sagittal (A) image shows a "flame-shaped" subchondral region of bone marrow edema-like signal in the cephalad aspect of the patella (arrow). Follow-up MRI 14 months later: T2-weighted sagittal (B) image now shows a subchondral region of well-circumscribed high signal intensity arising in the pre-existing bone marrow edema-like signal lesion (arrow). Note, the small full-thickness cartilage defect on the follow-up MRI (arrowhead).

association between marrow edema and subchondral cyst development. This longitudinal assessment of knee MR images in a selected cohort showed that subchondral cysts develop within regions of subchondral marrow edema-like signal and typically also subjacent to cartilage abnormalities in subjects with imaging evidence of osteoarthritis or progression of osteoarthritis.

Bone marrow edema-like signal in osteoarthritic knees represents a number of noncharacteristic histologic abnormalities[4]. Edema is not a major constituent of MRI signal intensity abnormalities in such knees thus the designation of bone marrow "edema-like" signal. Large bone marrow edema-like lesions on MRI are strongly associated with the presence of pain in knee osteoarthritis[7] and women with edema-like signal and full-thickness articular cartilage defects accompanied by adjacent subchondral cortical bone defects are more likely to have painful knee osteoarthritis[8]. Bone marrow edema-like signal is a potent risk factor for structural deterioration in knee osteoarthritis, and its relation to progression is explained in part by its association with limb alignment[9], which supports a biomechanical pathoetiology.

Proposed theories of the pathogenesis of subchondral cyst formation in osteoarthritis include bony microcontusions leading to necrosis, increased intra-articular pressure leading to extension of synovial fluid into the subchondral bone through tiny gaps in the articular surface (*Bone Contusion Theory*), or the proliferation of myxomatous tissue within the bone marrow (*Synovial Breach Theory*)[10].

Our longitudinal investigation is complementary to prior cross-sectional studies and longitudinal studies[3,4,7–9,11–13] showing that areas of bone marrow edema-like signal and subchondral cysts are not only associated with each other but support that bone marrow edema-like signal can be an early "pre-cyst" lesion. While not every area of bone marrow edema-like signal present gave rise to a cyst, the follow-up interval for some subjects was relatively short compared to the course of osteoarthritis and the imaging interval was sporadic. Alternatively, a subchondral cyst may not form because of a number of other factors that were not measured. The presence of subchondral cysts prompts the MRI reader to assess for defects in the overlying cartilage. However, it is not surprising that some cases do not show evidence of associated cartilage lesion. The lack of a simple biomechanical paradigm to explain the pathophysiology of subchondral cyst formation, as well as the intrinsic limitations in contrast and spatial resolution of MRI may account for these results. That is, the reason that not all subchondral cysts had MRI visible cartilage defects could be due to (1) inability of MRI to detect all cartilage abnormalities or (2) a full-thickness cartilage defect is neither necessary nor sufficient for subchondral cyst formation. Bone remodeling might contribute to subchondral cyst formation, particularly in absence of a full-thickness cartilage defect.

Although there may be coincidence between MRI and radiography regarding the presence of subchondral cysts in any given case, a significant discrepancy in sensitivity is expected between modalities. Whereas well-formed sclerotic reactive wall around cysts are often necessary for radiographic detection, the simple presence of a discrete fluid-like round structure in the subchondral bone suffices for MRI diagnosis. MRI identified subchondral cystic lesions appear discretely different than the ill-defined areas of edema-like signal. Hence there is concept validity that these represent cystic lesions. Construct validity has been shown in an investigation of knee osteoarthritis with MRI-histological correlation demonstrating that well-defined rounded areas of T2 fluid-like signal intensity had the highest proportion of cystic regions at histology[4].

The results of this investigation should be viewed within the limitations of the study design. This was a retrospective convenience sample with specific selection criteria in order to identify index cases of the condition of interest thereby introducing selection bias. We cannot comment on the overall incidence of bone marrow edema-like signal or subchondral cysts. In this study no correlation was attempted with clinical features. The grading system for osteoarthritis used represents an adaptation of the BLSA scale. This scale was developed for radiography and has been established as a useful scale for clinical epidemiological studies of knee osteoarthritis[6] but is not validated for MRI. We used this scale as a means of evidence to support that the findings identified are likely degenerative in origin but did not try to validate against radiography since these imaging studies were largely not available for this study population. More recently, MRI scales such as COAT (Comprehensive Osteoarthritis Assessment Tool)[14], WORMS (Whole-Organ Magnetic Resonance Imaging Score)[15], KOSS (Knee Osteoarthritis Scoring System)[16] and SFA-MR (French Society

of Arthroscopy-Magnetic Resonance score)[11] are being developed but validated scales were not available during the time of data collection for this investigation. We are using MRI as surrogate documentation of pathology for subchondral cysts since no histological confirmation was obtained. However, these are well-described phenomena that have characteristic and distinct appearances. The sample size was relatively small and the imaging intervals were sporadic limiting the epidemiological conclusions possible. Stratified analyses were not performed because they would be problematic and potentially misleading. Volumetric measurements are notoriously difficult particularly for bone marrow edema-like signal where the margins are often difficult to define. Our goal was to minimize variability by performing consensus measurements and applying formulas that would have systematic bias for all volumes calculated. The purpose was for this to be an efficacy study with the best possible interpretation. Observer variability is important but was not the intent of this investigation.

Future avenues for related research include developing a prospective cohort with uniform interval imaging over a longer period of time and with greater clinical correlation. This could be accomplished as a recruited opportunity sample such as the cohort being gathered by the National Institutes of Health Osteoarthritis Initiative (http://www.oai.ucsf.edu/) or from one of a number of osteoarthritis cohorts available: southeast Michigan Osteoarthritis cohort, the Veterans Health Study (VHS, a prospective observational study of health outcomes in 2425 veterans) or the Framingham Study. The time course of bone marrow edema-like signal to cyst conversion will be better assessed with the prospective longitudinal cohorts currently being gathered with routine time intervals of MRI. There may also be other non-imaging or imaging markers (such as meniscal positioning) for subchondral cyst formation. Arthroscopy correlation for characterizing cartilage lesions might also provide further insight.

This report serves as the initial determination of an association between two types of MRI identified subchondral reactions to joint degeneration and supports a temporal relationship between bone marrow edema-like signal and the pathogenesis of subchondral cysts. Further prospective investigations should be performed to validate these results.

References

1. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, *et al*. Guidelines for the medical management of osteoarthritis. Part I. Osteoarthritis of the hip. American College of Rheumatology (comment). Arthritis Rheum 1995;38(11):1535–40.
2. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum Aug 1998;41(8):1343–55.
3. Link TM, Steinbach LS, Ghosh S, Ries M, Lu Y, Lane N, *et al*. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. Radiology Feb 2003;226(2):373–81.
4. Zanetti M, Bruder E, Romero J, Hodler J. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. Radiology Jun 2000;215(3):835–40.
5. Bullough PG, Bansal M. The differential diagnosis of geodes. Radiol Clin North Am Nov 1988;26(6):1165–84.
6. Scott WW Jr, Lethbridge-Cejku M, Reichle R, Wigley FM, Tobin JD, Hochberg MC. Reliability of grading scales for individual radiographic features of osteoarthritis of the knee. The Baltimore longitudinal study of aging atlas of knee osteoarthritis. Invest Radiol Jun 1993;28(6):497–501.
7. Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM, *et al*. The association of bone marrow lesions with pain in knee osteoarthritis. Ann Intern Med Apr 3, 2001;134(7):541–9.
8. Sowers MF, Hayes C, Jamadar D, Capul D, Lachance L, Jannausch M, *et al*. Magnetic resonance-detected subchondral bone marrow and cartilage defect characteristics associated with pain and X-ray-defined knee osteoarthritis. Osteoarthritis Cartilage Jun 2003;11(6):387–93.
9. Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, *et al*. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med Sep 2, 2003;139(5 Pt 1):330–6.
10. Milgram JW. Morphologic alterations of the subchondral bone in advanced degenerative arthritis. Clin Orthop 1983;173:293–312.
11. Pessis E, Drape JL, Ravaud P, Chevrot A, Dougados M, Ayral X. Assessment of progression in knee osteoarthritis: results of a 1 year study comparing arthroscopy and MRI. Osteoarthritis Cartilage May 2003;11(5):361–9.
12. Beattie KA, Boulos P, Pui M, O'Neill J, Inglis D, Webber CE, *et al*. Abnormalities identified in the knees of asymptomatic volunteers using peripheral magnetic resonance imaging. Osteoarthritis Cartilage Mar 2005; 13(3):181–6.
13. Hayes CW, Jamadar DA, Welch GW, Jannausch ML, Lachance LL, Capul DC, *et al*. Osteoarthritis of the knee: comparison of MR imaging findings with radiographic severity measurements and pain in middle-aged women. Radiology Dec 2005;237(3):998–1007 (Epub Oct 26, 2005).
14. Biswal S, Hastie T, Andriacchi TP, Bergman GA, Dillingham MF, Lang P. Risk factors for progressive cartilage loss in the knee: a longitudinal magnetic resonance imaging study in forty-three patients. Arthritis Rheum Nov 2002;46(11):2884–92.
15. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, *et al*. Whole-Organ Magn Reson Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage 2004;12:177–90.
16. Kornaat PR, Ceulemans RY, Kroon HM, Riyazi N, Kloppenburg M, Carter WO, *et al*. MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS) – inter-observer and intra-observer reproducibility of a compartment-based scoring system. Skeletal Radiol 2005;34:95–102.