Magnetic resonance-detected subchondral bone marrow and cartilage defect characteristics associated with pain and X-ray-defined knee osteoarthritis

M. F. Sowers Ph.D.†*, C. Hayes M.D.‡, D. Jamadar M.D.‡, D. Capul B.A.†, L. Lachance Ph.D.†, M. Jannausch M.S.† and G. Welch Ph.D.†

†Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, USA
‡Department of Radiology, University of Michigan, Ann Arbor, MI, USA

Summary

Objective: To assess whether the presence of subchondral bone marrow abnormalities (bone marrow edema (BME)) and cartilage defects, determined by magnetic resonance imaging (MRI), would explain the difference between painful osteoarthritis of the knee (OAK) compared with painless OAK or pain without OAK.

Method: Four groups of women (30 per group), aged 35–55 years, were recruited from the southeast Michigan Osteoarthritis cohort (group 1: painful OAK, group 2: painless OAK, group 3: knee pain without OAK, and group 4: no OAK or knee pain). OAK was defined by a Kellgren–Lawrence score of 2 or greater, while pain was based on self-report. BME and cartilage defects were identified from MRI.

Results: BME lesions were identified in 56% of all knees. BME lesions were four times (95% CI=1.7, 8.7) more likely to occur in the painless OAK group compared with the group with pain, but no OAK. BME lesions >1 cm were more frequent (OR=5.0; 95% CI=1.4, 10.5) in the painful OAK group than all other groups. While the frequency of BME lesions was similar in the painless OAK and painful OAK groups, there were more lesions >1 cm in the painful OAK group.

About 75% of all knees had evidence of some cartilage defect, of which 35% were full-thickness defects. Full-thickness cartilage defects occurred frequently in painful OAK. One-third of knees with full-thickness defects and 47% of knees with cartilage defects involving bone had BME >1 cm. Women with radiographic OA, full-thickness articular cartilage defects, and adjacent subchondral cortical bone defects were significantly more likely to have painful OAK than other groups (OR=3.2; 95% CI=1.3, 7.6).

Conclusion: The finding on MRI of subchondral BME cannot satisfactorily explain the presence or absence of knee pain. However, women with BME and full-thickness articular cartilage defects accompanied by adjacent subchondral cortical bone defects were significantly more likely to have painful OAK than painless OAK.

Key words: Osteoarthritis, Pain, Magnetic resonance imaging, Bone marrow edema, Cartilage defects, Subchondral bone.

Introduction

Although osteoarthritis (OA) is highly prevalent, affecting up to 70% of the population over the age of 65 years, pain is the symptom that drives much of the disability, choice of therapy, and health-care costs. However, clinically and epidemiologically, it is well recognized that individuals may have radiographic evidence of OA of the knee (OAK), including evidence of compromised articular cartilage and subchondral bone without pain symptoms. Likewise, individuals may have painful knees without radiographic evidence of OAK. Thus, X-ray-defined OAK is not synonymous with knee joint pain.

There is limited understanding of how pain patterns are linked to the compromises in bone, cartilage, and other soft tissues of the knee in OA, particularly in the absence of a known injury. This is due, in part, to the limitations of conventional radiography, the most commonly used imaging modality. Conventional radiography permits only limited assessment of the three knee compartments, provides only an approximation of articular cartilage change with measurement of joint space narrowing, and poorly characterizes the quantitative changes in soft tissue, cartilage, and subchondral bone, and have related those changes to pain patterns. The cause(s) of painful OAK is unclear. While there is change in hyaline articular cartilage with OA, with an initial period of hypertrophy followed by loss, cartilage does not have pain fibers. In contrast, bone and bone marrow are rich in nociceptive fibers, suggesting that bone could contribute to the pain profile. MR-detected focal signal abnormalities in the trabecular bone marrow, or bone marrow...
edema’ (BME), have been well documented in numerous painful osseous conditions, such as transient osteoporosis\textsuperscript{10}, stress fractures\textsuperscript{11}, and osteonecrosis\textsuperscript{10,12}, and have been proposed as one potential source of knee joint pain in OAK. In painful osseous conditions, it is hypothesized that BME represents the accumulation of extracellular fluid in the marrow and leads to increased intraosseous pressure\textsuperscript{12}. This could affect signaling from nociceptors, giving rise to heightened pain. Mechanically reducing intraosseous pressure appears to relieve pain in some sufferers\textsuperscript{13}.

To relate these events to a hypothesis of painful OAK, a subchondral bone marrow signal abnormality, observable only with MRI and thought to be BME, could be associated with the development of increased intraosseous pressure and a heightened pain response. The BME may be due to mild cellular injury, possibly induced by microtrauma resulting from mal-distributed weight-bearing forces. We hypothesized that the capacity to quantify the amount of subchondral bone marrow signal abnormality (BME) would allow us to more fully explain the aberration of self-reported joint pain in the apparent absence of radiographically defined OA among mid-aged women. Therefore, we sampled women from four possible pain/OAK groups and compared the frequency of BME and cartilage defects between groups. The contrasting pair-wise groups of particular interest were those with and without painful OA, as well as those who had painless OAK vs those who had pain without OA.

Materials and methods

POPULATION

A two-factor balanced study design was used to test the hypothesis with enrollees identified from the southeast Michigan (SEM) OA cohort. The SEM cohort includes 543 women from the Study of Women’s Health Across the Nation (SWAN, Michigan Center) and 510 women from the Michigan Bone Health Study (MBHS), with all enrollees being assessed for OA using X-rays and interviews in identical protocols\textsuperscript{14}. From the SEM OA cohort of 843 women over the age of 40 years, four pain/OAK groups consisting of 30 women per group were recruited on the basis of co-occurrence of pain (reported in the 1998 knee joint pain interview) and OA (Kellgren–Lawrence (K–L) summary score ≥2 from the 1998 AP weight-bearing knee X-rays). The four groups were: group 1—painful radiographic OAK; group 2—painless radiographic OAK; group 3—no radiographic OA but knee joint pain; and group 4—no radiographic OA or knee joint pain. The absolute frequency of the four groups in the SEM population is shown in Table I. Women were not recruited on the basis of the absolute frequency of pain/OAK in the parent population, but according to a study design that would provide enough statistical power to efficiently compare MRI characteristics in the four groups. Approximately 10 extra women in each group were selected for recruitment, recognizing that some women would elect not to participate or would be ineligible because of embedded metal. Prior to MRI scanning, women were interviewed to ascertain if they had debilitating claustrophobia, embedded or non-removable body metal, or recent imaging studies.

Both the 1998 evaluation of the SEM and this substudy were organized under the provisions of the University of Michigan Institutional Review Board.

<table>
<thead>
<tr>
<th>Knee joint pain</th>
<th>Knee OA (X-ray)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>10%</td>
</tr>
<tr>
<td>No</td>
<td>5%</td>
</tr>
</tbody>
</table>

OA ASSESSMENT

MRI of both knees was performed individually by knee using a 1.5 T (GE Sigma, GE Medical Systems, Milwauke, WI) scanner equipped with a knee surface coil. The specific sequences included sagittal, coronal, and axial fast spin echo (FSE) proton density (PD) with fat saturation (FS) sequences (TR 4000 ms, TE 15 ms, 4 mm thickness), sagittal spin echo (SE) PD (TR 1000 ms, TE 14 ms, 3 mm thickness), and sagittal 3-D spoiled gradient echo (SPGR) with FS (TR 38 ms, TE 6.9 ms, flip angle (FA) 45°, 2 mm effective thickness)\textsuperscript{14–16}. FOV was between 12 and 14 cm. The FSE PD FS sequences were chosen to secure excellent tissue contrast between articular cartilage, bone, and fluid, enabling assessment of cartilage defects and excellent signal to noise ratio (S/N) for evaluation of periarticular soft tissues. The fluid-weighted characteristics of FSE PD FS allowed detection of subchondral marrow signal changes thought to be BME (Figs. 1 and 2). Total imaging time per knee was approximately 35 min.

Each of the three knee compartments was evaluated by two experienced musculoskeletal radiologists for the presence of cartilage defects and BME. BME was defined on FSE PD FS images as subchondral signal abnormalities showing increased signal compared with adjacent marrow and skeletal muscle, but without a defined rim or homogenous fluid appearance as seen with cysts. The presence of BME was graded by size (width of lesion, measured perpendicular to the adjacent articular surface) on a 0–2 scale (0, none; 1, less than 1 cm; 2, greater than 1 cm). Cartilage defects were scored on the basis of depth (0, 0–49, 50–99, 100%), and size (area in cm\textsuperscript{2}), using a modified classification system based on the classification adopted by Drape et al.\textsuperscript{17}. In addition, any ulceration or defect of the subchondral cortex beneath a cartilage defect was identified by the readers.

Following an initial calibration to generate comparable measures of lesions, each radiologist read the images separately. Then, the readings were compared and consensus readings undertaken to reconcile discordant readings (κ=0.85). These consensus readings took place over a 30-day period, helping to preclude the likelihood of drift over time. The readers were blinded as to the group assignment of the scans being read.

RADIOGRAPHS

Anterior–posterior knee radiographs had been taken in a weight-bearing position in both SEM populations. Technicians used X-ray equipment Model X-GE MPX-80 (General Electric Co. Medical Systems Division, Milwaukee, WI) and X-DA film with Kodak rare earth intensifying screens (Eastman Kodak, Rochester, NY). The source film distance was 40 inches, and standard radiographic techniques were used.
Evaluation for radiographically defined OA was undertaken by blinded investigators (MSK radiologist and rheumatologist), using the Kellgren and Lawrence system shown in the Atlas of Standard Radiographs of Arthritis, a standardized scoring approach that has been previously described. This system is a summary score incorporating information about osteophyte formation, joint space narrowing, sclerosis, and joint deformity characteristics. Joints are classified according to the five-level scale labeled as: 0, normal; 1, doubtful OA; 2, minimal OA; 3, moderate OA; or 4, severe OA.

PAIN ASSESSMENT

The 1998 pain assessment, using the questions for both knees derived from the Tecumseh Community Health Study, was used as one of the requirements for group assignment. Because pain is transitory, it was also assessed as the day of MRI measurement, when women were asked to rate pain in each knee on a 10-point scale and identify the location of the pain within the knee. The relative number of women reporting pain in the previous 24 h was consistent with the designed groupings based on pain, so those groups were retained in the data analysis. The frequency of pain in the previous 24 h ascertained at time of MRI was as follows: 3% in the no pain, no OAK group; 14% in the OAK but no pain group; 32% in the no OAK but pain group; and 38% in the OAK and pain group.

DATA ANALYSIS

Table I shows characteristics by woman. Individual knees were the unit of analysis for the study data. It is recognized that two knees on a single woman may not represent independent events, an underlying assumption of most approaches of data analysis. To overcome this, data were analyzed using statistical procedures that allowed us to account for the autocorrelation with knees within a woman. Eight knee scans from five women were excluded from analyses, as the injury history recall indicated OAK from trauma. A ninth scan was omitted due to suboptimal imaging.

An analysis of variance approach was used to calculate and compare the mean values of the continuous variables, including age and body mass index (BMI). Contingency table analyses and logistic regression analyses were used to determine the odds of having BME associated with knee joint pain or OAK. Logistic regression analyses were used to test the hypothesis by comparing the group with only knee pain with the group with painless radiographically defined OAK, and comparing the frequency of BME in women with painless OAK with the women with painful OAK. The same approach was used to evaluate the role of cartilage defects. Finally, logistic regression analysis and contingency table analyses were used to describe the combined association of BME and cartilage defects in relation to the difference between painful OAK vs painless OAK. Goodness-of-fit statistics, such as the Hosmer-Lemeshow statistic or other χ² statistics, were applied. Statistical analysis was completed with SAS 8.0. Statistical significance was demonstrated with the use of P-values and 95% confidence intervals (95% CI).

Results

In the SEM parent population of women aged 40–55 years (Table I), there were 5% of women who were classified as having OAK on X-ray, but reported no pain in the month prior to X-ray. Further, one-third of all women reported knee joint pain in the previous month, but these women did not have radiographically defined OAK. An equal number of women from the four possible pain/OAK groups were sampled for study with MRI to illuminate two contrasts. The first contrast was to identify differences in BME and cartilage defects in those with and without painful OA. The second contrast was to identify the difference in BME and cartilage defect frequency in those who had painless OAK vs those who had pain without OAK.
DESCRIPTION OF STUDY ENROLLEES

Table II shows selected characteristics of women in each of the four groups. Women with OAK were significantly heavier than women without OAK, as evidenced by measures of both weight and BMI ($P<0.0004$). The mean BMI of women with painful OAK was comparable with the mean BMI of women with OAK without pain (32.7 kg/m$^2$±0.4 vs 33.0±0.4, $P<0.74$). There were no differences in age, smoking behavior, or frequency of knee injury among the groups (data not shown).

BME LESIONS

Hyper-intense signals thought to be BME lesions were common (see Table II). For example, one-third of the normal comparison group (women classified as having no OAK and no pain) had BME lesions in at least one knee, though the lesions were usually less than 1 cm in size. In this sample, there were 16% of knees (N=38) with BME lesions greater than 1 cm in size, 40% of knees (N=93) with BME lesions less than 1 cm in size, and 44% of knees with no BME.

Table II shows the distribution of BME lesions according to group. BME lesions of any size occurred frequently in knees of women with radiographically defined OAK (OR=4.3, 95% CI=2.6, 7.3). Only one-quarter of women’s knees in the OAK groups had no evidence of BME lesions, while 53 and 65% of knees in the two non-OAK groups, respectively, had no evidence of BME.

BME with lesions size of 1 cm or greater were significantly more frequent (OR=5.0, 95% CI=2.4, 10.5) in the group with painful OA than in the other groups, including the group with painless OA (OR=4.3, 95% CI=1.7, 8.7) more frequently in knees with X-ray-defined OAK, but no pain (41/54 (76%)) as compared with knees that had pain, but no OAK (26/58 (45%)) $P=0.001$.

CARTILAGE DEFECTS

In this sample, there was substantial evidence of cartilage defects. Only 25% of knees (N=58) were visualized as having cartilage free of defects. The frequency of full-thickness cartilage defects was much less common. There were 82 knees (35%) with a cartilage defect that penetrated to the bone surface, and slightly less than half of these full-thickness defects included bone ulceration.

Approximately three-fourths of knees from women without OA had normal cartilage or only mild defects, while less than a quarter of knees from groups with radiographically defined OAK had normal cartilage or only mild defects. Knees in the group with painful OA were most likely to have full-thickness cartilage defects, and most of these defects included bone ulceration (Table II). The primary difference between knees with and without painful OA was amount of bone ulceration that accompanied the full-thickness cartilage defect (Fig. 4).

SIGNIFICANT BME AND CARTILAGE DEFECTS

Women with >1 cm BME lesions were more likely to have prominent cartilage defects. Few knees (11/149 (7%)) with
normal cartilage or a cartilage defect that did not penetrate to bone had a BME >1 cm in size. In contrast, 33% of knees (16/48) with a cartilage defect penetrating to the bone had a BME >1 cm in size, and 47% of knees (16/34) with a cartilage defect that included a bone ulcer had a BME >1 cm in size ($P<$0.0001). As shown in Fig. 5, knees that had painful OAK were more likely to have full-thickness cartilage defects accompanied with bone ulceration and BME compared with knees in which there was painless OAK ($P<$0.05).

Discussion

We hypothesized that quantifying the frequency of BME and focal cartilage defects would allow us to explain the conundrum of self-reported joint pain in the apparent absence of radiographically defined OA, an aberration that has been noted by other researchers. Skeptics have questioned whether the aberration arises because of different perceptions or sensitivity to pain, because of errors in reading radiographs, because the pain is a reflection of other co-morbid conditions, or if the pain is a function of the severity of OA or its progression.

This study confirms the clinical perception that self-reported knee joint pain occurs in the absence of radiographically defined OA, even in a younger population of women. In this sample, BME and cartilage defects did not explain difference in the pain vs no pain groups. BME was not associated with pain in the absence of OA. However, larger BME (>1 cm) lesions coupled with cartilage defects that penetrated to and included subchondral bone were elements that had markedly greater frequency in the painful OAK group compared with the non-painful OAK group. These findings are consistent with the pathophysiological model proposed for this study.

Our work confirms and extends the findings from a recent study that reported more BME among persons with both OA and pain than among persons with OA, but without pain. The enrollees from that study, largely from the Veterans Administration system, were elderly and probably more ill than the general population. Those findings were based on a cross-sectional observation, and like our data, cannot address the temporal aspects of pain and BME.

![Image](image-url)
However, that report did not address the likelihood that BME must be linked with other structural changes in bone or cartilage to be associated with pain.

Although the presence of BME, cartilage defect, and bone ulceration appears to be promising as a marker of painful OA, there are a number of issues yet to be resolved, including a clear elucidation of the nature of BME. Wilson et al.24 first used the term ‘bone marrow edema’ in describing bone marrow signal changes in transient osteoporosis of the hip. MR signal abnormalities consisting of low signal on T1W images and increased signal on heavily T2-weighted images are not specific, and can be seen in the marrow space in numerous non-neoplastic diseases, including stress fractures, infection, OA, and inflammatory arthropathies.29 Supporting the likelihood that both mechanisms may occur during cyst formation, and we propose a similar mechanism for subchondral BME changes in OA.

Broader, less defined, and less intense subchondral marrow changes are more difficult to explain on the basis of these existing theories. In a histologic study of specimens taken from knees undergoing total joint replacement, Zanetti et al.30 failed to find evidence of significant ‘edema’ in tibial plateau specimens resected during total knee arthroplasties. Instead, they reported histologic evidence of fibrosis, marrow necrosis, and abnormal trabeculae, especially near the articular surface and in areas corresponding to better defined signal changes. The more distant and ill-defined lesions showed little histologic changes with no evidence of increased edema. It should be noted that the histologic diagnosis of ‘edema’ is relatively crude, relying on secondary signs that are not sensitive. New, water-sensitive MR sequences may show signal abnormalities related to minimal local changes in extracellular water that are undetected by routine histologic examination.

The relatively high frequency of BME-like lesions in the control group with no pain/no OA is surprising and not readily interpreted. It is uncertain if these hyper-intensive signals represent BME, other pathology, or even an indicator of changes that are a precursor to pathology. Because pain and X-ray-defined OA were identified approximately 6 months prior to MRI, this might even represent developing OA in some of the women. The high frequency provides additional motivation for longitudinal study of BME to identify those characteristics that precipitate these lesions.

Because this is a cross-sectional study design within a longitudinal study, we cannot identify if and how quickly the BME will resolve and if resolution is a function of the degree of bone ulceration and its association with pain. Also, we cannot determine if those women with X-ray-defined OA and no pain will progress to having pain, based on the presence of BME, full-thickness cartilage defect, and bone ulceration. We have not linked BME lesions to measures of mal-distributed weight-bearing forces. This would include the measurement of varus and valgus and the use of gait analysis. Finally, because this is not a clinical trial, we cannot identify how BME, cartilage defect, and bone ulceration will respond to current therapies, including those that address pain, inflammation, or bone deterioration. These issues should be addressed before information about BME and full-thickness cartilage defects with bone ulceration become the targets of clinical interventions.

In summary, the currently reported experience suggests that BME associated with a full-thickness cartilage defect and bone ulcer is most consistently observed with knee joint pain. The fact that MRI allows for assessment of BME and cartilage defects, which is not possible with other techniques, is highly relevant in that its use may expand our understanding of the pain associated with OA beyond what can currently be determined with clinical examination. Further investigation is necessary to understand the precise nature of BME and its potential value as a marker of pain in OA.

References


