Bone Marrow Edema and Its Relation to Progression of Knee Osteoarthritis

David T. Felson, MD, MPH; Sara McLaughlin, MPH; Joyce Goggins, MPH; Michael P. LaValley, PhD; M. Elon Gale, MD; Saara Totterman, MD; Wei Li, MBA; Catherine Hill, MD, MSc; and Daniel Gale, MD

Background: **While factors affecting the course of knee osteoarthritis are mostly unknown, lesions on bone scan and mechanical malalignment increase risk for radiographic deterioration. Bone marrow edema lesions on magnetic resonance imaging correspond to bone scan lesions.**

Objective: **To determine whether edema lesions in the subarticular bone in patients with knee osteoarthritis identify knees at high risk for radiographic progression and whether these lesions are associated with limb malalignment.**

Design: **Natural history study.**

Setting: **A Veterans Administration hospital in Boston, Massachusetts.**

Patients: **Persons 45 years of age and older with symptomatic knee osteoarthritis.**

Measurements: **Baseline assessments included magnetic resonance imaging of the knee and fluoroscopically positioned radiography. During follow-up at 15 and 30 months, patients underwent repeated radiography; at 15 months, long-limb films were obtained to assess mechanical alignment. Progression was defined as an increase over follow-up in medial or lateral joint space narrowing, based on a semi-quantitative grading. Generalized estimating equations were used to evaluate the relation of medial bone marrow edema lesions to medial progression and lateral lesions to lateral progression, before and after adjustment for limb alignment.**

Results: **Of 256 patients, 223 (87.1%) participated in at least one follow-up examination. Medial bone marrow lesions were seen mostly in patients with varus limbs, and lateral lesions were seen mostly in those with valgus limbs. Twenty-seven of 75 knees with medial lesions (36.0%) showed medial progression versus 12 of 148 knees without lesions (8.1%) (odds ratio for progression, 6.5 [95% CI, 3.0 to 14.0]). Approximately 69% of knees that progressed medially had medial lesions, and lateral lesions conferred a marked risk for lateral progression. These increased risks were attenuated by 37% to 53% after adjustment for limb alignment.**

Conclusion: **Bone marrow edema 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.**

Ann Intern Med. 2003;139:330-336. www.annals.org

For author affiliations, see end of text.

Osteoarthritis, the most common form of arthritis, is the leading cause of mobility-related disability in elderly persons (1). With the aging of the population, the prevalence of osteoarthritis is increasing. Loss of hyaline articular cartilage is a central pathologic event in osteoarthritis, but the pathogenesis of cartilage loss is poorly understood. Specifically, there is a paucity of information about what factors identify joints at high risk for progression. Identification of such factors might permit better understanding of the disease process.

While cartilage loss is a major pathologic feature of osteoarthritis, abnormal bone has been documented as another important element. Bone scan studies of persons with osteoarthritis have reported late-phase uptake of tracer in subchondral bone, signifying accelerated bone turnover. This increase in tracer has been associated with joint pain (2) and with a markedly increased risk for radiographic progression in osteoarthritis of the knee (3) and hand (4). The study in knees, however, was limited by the use of outdated radiographic techniques (5).

Increased uptake on bone scan has a parallel finding on magnetic resonance imaging (MRI): bone marrow edema (6, 7). Bone marrow edema is indicated by focally increased signal in the marrow on fat-suppressed T2-weighted images. McAlindon and colleagues (7) found that of 12 knees with bone scan lesions, 11 had bone marrow edema lesions in the same location. The question of whether bone marrow edema lesions on MRI affect structural change in the osteoarthritic joint has not been longitudinally evaluated. We previously reported that among persons with radiographic knee osteoarthritis, those with bone marrow edema lesions more often had knee pain than those without (8). In patients without osteoarthritis, these edema lesions have been associated with bone trauma (9, 10).

Like lesions on bone scans, limb malalignment has also been reported as a potent risk factor for structural progression of osteoarthritis. In a recent longitudinal study (11), patients with varus alignment were at high risk for subsequent medial progression of knee osteoarthritis, while limbs with valgus alignment were at commensurately high risk for lateral progression. The accepted mechanism for the effect of malalignment is that increased stress on one side of the joint leads to cartilage loss.

We performed a natural history study of knee osteoarthritis using MRIs and knee radiography. One goal of our study was to examine the effect of bone marrow edema lesions on structural deterioration of the joint, as indicated by joint space loss on radiographs. Previous work (12) documented the correlation between joint space width and articular cartilage thickness, and other studies (11, 13) have used joint space loss as a proxy for cartilage loss. Our objectives were to investigate the relation of bone marrow

Context

Bone marrow edema on magnetic resonance imaging (MRI) correlates with pain in patients with knee osteoarthritis, but its association with progression of joint changes is unknown.

Contribution

Among 223 patients with knee osteoarthritis, bone marrow edema on MRI was associated with radiographic progression in the same compartment over the following 15 to 30 months after adjustment for age, sex, body mass index, and limb malalignment (another predictor of progression).

Cautions

While this study shows that bone marrow edema is associated with the progression of knee osteoarthritis, we do not know whether it is causal or an epiphenomenon. These findings do not define a role for MRI in the routine evaluation of knee osteoarthritis.

–The Editors

edema lesions to joint space loss in patients with osteoarthritis, to evaluate whether these lesions were associated with malalignment, and to determine whether some of the relation of marrow lesions to progression could be explained by their association with malalignment. In addition, if bone marrow edema lesions were associated with malalignment, we postulated that they had a local effect and that the contralateral side of the joint was protected.

METHODS

Patients were recruited to participate in a natural history study of symptomatic knee osteoarthritis. All patients in the current study are a subset of patients whose recruitment has been described in detail elsewhere (8). Briefly, patients were recruited from two prospective studies, one in men and one in women, of quality of life among veterans; from clinics at Boston Medical Center in Boston, Massachusetts; and from advertisements in local newspapers. Potential participants were asked two questions: "Do you have pain, aching, or stiffness in one or both knees on most days?" and "Has a doctor ever told you that you have knee arthritis?" For patients who answered yes to both questions, we conducted a follow-up interview in which we asked about other types of arthritis that could cause knee symptoms. If no other forms of arthritis were identified, then the individual was eligible for recruitment. A series of knee radiographs were obtained for each patient to determine whether radiographic osteoarthritis was present. If patients had a definite osteophyte on any view in the symptomatic knee, they were eligible for the study. Because they had frequent knee symptoms and radiographic osteoarthritis, all patients met American College of Rheumatology criteria for symptomatic knee osteoarthritis (14).

For the natural history study, we enrolled patients who were interested in participating and who could walk with or without a cane. Of 351 patients from the cross-sectional study (8), 324 met these criteria. Of these, 193 men and 19 women received care from the Veterans Administration Health Care System and were recruited from the outpatient clinics there. Eight men and 104 women were recruited from the community.

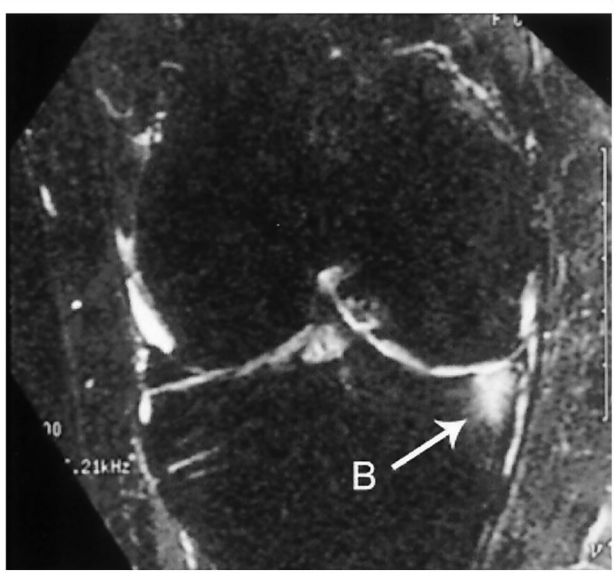
The study included a baseline examination and follow-up examinations at 15 and 30 months. At baseline, patients who did not have contraindications to MRIs had MRI of the more symptomatic knee. At all examinations, patients had knee radiography and answered questionnaires about the severity of knee symptoms, including the Western Ontario McMaster Osteoarthritis (WOMAC) questionnaire. Patients were also weighed, with shoes off, on a balance-beam scale, and height was assessed. At the first follow-up visit, long-limb films were obtained with a 14 × 51 cassette, using methods described elsewhere (15). Our study focuses on baseline MRI findings as predictors of change in radiographs over follow-up. The institutional review boards of Boston University Medical Center and the Veterans Administration Boston Health Care System approved the baseline and follow-up examinations.

Assessments

Magnetic Resonance Imaging

All studies were performed with a Signa 1.5T MRI system (General Electric Corp., Milwaukee, Wisconsin) using a phased-array knee coil. A positioning device was used to ensure uniformity among patients. Coronal, sagittal, and axial images were obtained. Coronal spin-echo fat-saturated proton density and T2-weighted fat-saturated

Figure 1. **Bone marrow edema lesion (*B*) on magnetic resonance imaging.**



This lesion was scored as grade 2 in size on a scale of 0 to 3.

images (repetition time, 2200 milliseconds; echo time, 20/80 milliseconds) with a slice thickness of 3 mm, a 1-mm interslice gap, one excitation, a field of view of 11 to 12 cm, and a matrix of 256 × 128 pixels were obtained.

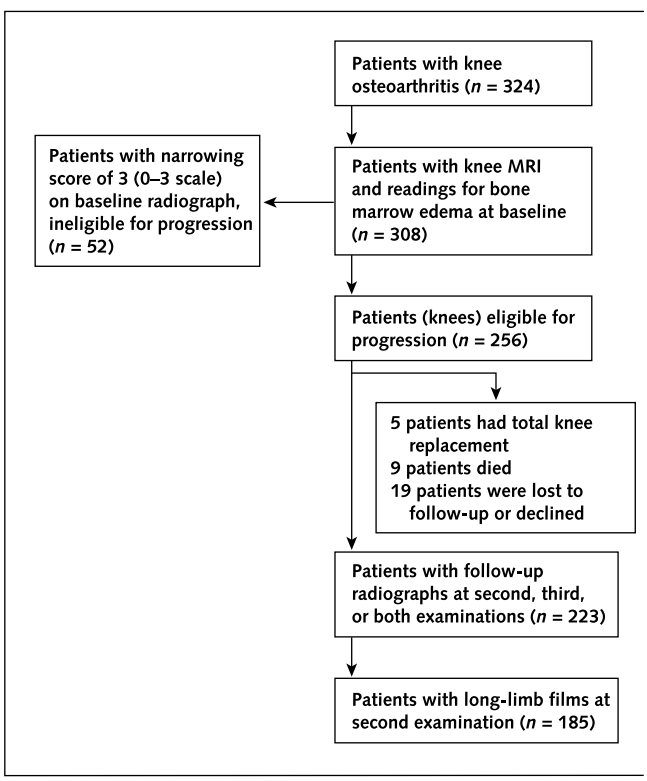
To evaluate bone marrow lesions, we used the coronal T2-weighted fat-saturated images. As previously reported (8), each femur and tibia were divided into medial, central, and lateral quadrants, resulting in six potential sites of lesions for each knee. We defined lesions as areas of increased signal adjacent to the subcortical bone; a single radiologist, blinded to patient characteristics and radiographs, graded lesions from 0 to 3 on the basis of their size. Because previous work (8) demonstrated that lesions of grade 2 or greater were more strongly associated with the presence of knee pain (grade 1 lesions were common in those with and without knee pain), we focused on lesions that were grade 2 or larger. Such lesions encompassed at least one quarter of the width of the compartment on two or more slices (**Figure 1**). For intraobserver agreement for reading of these lesions, the κ value was 0.66 ($P < 0.001$). We defined a lesion as occurring in either the medial or lateral compartment if it was present in the femur or tibia of that compartment.

Radiography

Patients underwent weight-bearing posteroanterior radiography using the protocol of Buckland-Wright (16). Using fluoroscopic positioning, we aligned the beam relative to knee center, and the knee was flexed so that the anterior and posterior lips of the medial tibial plateau were superimposed. Feet were rotated until the tibial spines were centered in the notch, and outlines of foot rotation were then made on foot maps so that the foot rotation would be the same for subsequent films. Fluoroscopic positioning has been shown to more accurately assess joint space compared with nonfluoroscopic acquisition and to improve reproducibility of joint space assessment. Other films obtained at baseline included weight-bearing skyline (17) and weight-bearing semi-flexed lateral films; the latter were obtained according to the Framingham Study protocol.

For evaluation of progression, we focused on the width of the joint space in medial and lateral compartments, since that has been found to correlate with cartilage thickness (12). Films were read by using the Osteoarthritis Research Society International Atlas (18), in which each medial and lateral tibiofemoral joint space is graded from 0 (normal) to 3 (bone on bone). We defined progression of joint space narrowing in a knee compartment as progression by at least one grade. A reader unfamiliar with the MRI findings read all films. All films were read unblinded to sequence; however, films for a subsample of patients were also read blinded to sequence to test the reproducibility of progression measurement and to evaluate possible bias in characterizing progression. Unlike previous cross-sectional studies, in which agreement was most relevant for one point in time, we were interested primarily in studying change on radiographs and therefore tested agreement in evaluating progression between films that were blinded to sequence and those that were unblinded. For intraobserver agreement for reading progression, the κ value was 0.81 ($P < 0.001$), and disagreements between blinded and unblinded readings were in no particular direction, that is, there was no greater tendency for unblinded readings to be read as showing progression.

Figure 2. **Flow of patients through the study.**



MRI = magnetic resonance imaging.

Other Measures

Mechanical alignment, assessed at the first follow-up examination, was measured in degrees on a continuous scale, with values less than 0 representing valgus alignment, values of 0 representing neutral alignment, and values greater than 0 representing varus alignment. For interobserver agreement for reading alignment, the intraclass correlation coefficient was 0.97 ($P < 0.001$).

Statistical Analysis

Patients who were eligible for the current study underwent MRI at baseline in which the knee imaged did not have grade 3 joint space narrowing at baseline. We compared those who had at least one radiograph on follow-up examination with those who had none by using the chi-square test for dichotomous variables, the *t*-test for contin-

Table 1. **Characteristics of Patients Who Participated in Follow-up Compared with Those Who Were Not Followed***

Characteristic	Followed ($n = 223$)	Not Followed ($n = 33$)	*P* Value
Age, *y*	66.2 ± 9.4	67.8 ± 9.6	>0.2
Women, %	41.7	15.2	0.003
BMI, kg/m^2	31.1 ± 5.8	31.0 ± 6.0	>0.2
Weight, *kg*	191.5 ± 38.3	200.3 ± 40.7	>0.2
WOMAC pain score (range, 0–20)	6.9 ± 3.6	9.1 ± 4.7	0.02
WOMAC disability score (range, 0–68)	23.4 ± 11.2	30.2 ± 16.4	0.03
Mechanical alignment, *degrees*	2.8 ± 5.0†	NA	
Medial bone marrow edema lesions, %	33.6	45.5	0.18
Lateral bone marrow edema lesions, %	17.9	15.2	>0.2
Kellgren–Lawrence grade, %			
0	5.8	9.1	>0.2
1	19.3	15.2	
2	20.2	30.3	
3	44.4	39.4	
4	10.3	6.1	
Follow-up at first follow-up examination only, *n (%)*	25 (11.2)	NA	
Follow-up at study end, *n (%)*	198 (88.8)	NA	

* Values presented with plus/minus signs are means ± SD. BMI = body mass index; NA = not available; WOMAC = Western Ontario McMaster Osteoarthritis questionnaire.
† A positive value indicates that the mean is in a varus direction.

uous variables, and the Wilcoxon rank-sum test for ordinal variables (19).

To test the relation of bone marrow lesions to mechanical alignment, we grouped the limbs according to quartile of mechanical alignment and tested for an association by performing two logistic regression analyses with medial and lateral lesions, respectively, as dependent variables and alignment as the independent variable. To evaluate the relation between bone marrow edema lesions and compartment-specific progression, we first laid out simple tables testing whether knees with lesions had higher rates of progression than knees without lesions at the first or second follow-up examinations. We tested ipsilateral (for example, medial lesions leading to medial progression) and contralateral (for example, medial lesions leading to lateral progression) effects. Because repeated radiographic assessments were performed during follow-up, and because we wanted to control for confounders such as age, sex, and body mass index, we ultimately performed logistic regression analyses in which the referent dependent variable was no radiographic progression. To adjust for correlated data over time in individual patients, we used generalized estimating equations (20).

One of the goals of our study was to evaluate whether an association with alignment explained the effect of bone marrow edema lesions. To evaluate this, we used the same logistic regression analyses described earlier to test whether the relation of marrow edema with progression was attenuated after alignment was added as an independent variable, comparing the odds ratio associating bone marrow edema lesions with progression before and after adjustment for alignment. We defined a significant attenuation of the relation as at least a 10% decrease in the odds ratio (21). Results were unchanged in additional analyses in which we adjusted for the severity of pain in the knee (using a visual analogue scale pain measure). All *P* values reported are two-sided.

Role of the Funding Sources

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Two hundred fifty-six patients, each with one knee studied, met our inclusion criteria (**Figure 2**). Of these, 223 (87.1%) had at least one follow-up examination with a radiographic assessment. **Table 1** compares the baseline characteristics in those followed versus those lost to follow-up. Those lost to follow-up did not differ substantially from the other participants in age, weight, or prevalence of bone marrow lesions but were more likely to be men and to have higher WOMAC pain and disability scores at baseline. Of the 33 patients characterized as lost to follow-up, 5 came to the follow-up examinations but had undergone

Table 2. **Relation of Bone Marrow Edema Lesions to Mechanical Alignment***

Alignment	Knees with Medial Lesions, %	Knees with Lateral Lesions, %
Quartile 1 (alignment ≤ 0 degrees, most valgus)†	16.4	29.5
Quartile 2 (alignment 1–3 degrees)	18.8	16.7
Quartile 3 (alignment 4–6 degrees)	40.0	6.7
Quartile 4 (alignment ≥ 7 degrees, most varus)	74.3‡	8.6§

* Based on 189 knees.
† Alignment ≤ 0 degrees includes neutral alignment and all limbs that were valgus; alignments for quartiles 2–4 are all varus limbs.
‡ $P < 0.001$ for trend.
§ $P = 0.002$ for trend.

Table 3. **Bone Marrow Edema Lesions and Their Relation to Ipsilateral Radiographic Progression**

Variable	Knees with Progression on Side of Lesion, *n/n (%)*	Adjusted Odds Ratio for All Patients in the Longitudinal Analysis (95% CI)*
Medial progression		
Medial lesion	27/75 (36.0)	6.5 (3.0–14.0)
No medial lesion	12/148 (8.1)	1
Lateral progression		
Lateral lesion	10/40 (25.0)	6.1 (2.2–16.5)
No lateral lesion	10/183 (5.5)	1

* Adjusted for age, sex, and body mass index. Odds ratios (95% CI) for these variables were as follows for medial progression and lateral progression, respectively: age (per year), 1.0 (0.9–1.0) and 1.1 (1.0–1.1); sex (women), 0.8 (0.4–1.8) and 3.1 (1.1–8.8); body mass index (per unit), 1.1 (1.0–1.1) and 1.0 (0.9–1.1).

total replacements of their study knees. Four additional patients had had their study knees replaced by the second follow-up visit; however, because radiographic follow-up was obtained at the first follow-up visit, these patients were included as having been followed.

We found a striking association between bone marrow edema lesions and mechanical alignment (**Table 2**). Limbs with varus alignment, especially if marked (≥7 degrees), had a remarkably high prevalence of medial lesions compared with limbs that were neutral or valgus (74.3% vs. 16.4%; $P < 0.001$ for relation between alignment and medial lesions). Conversely, limbs that were neutral or valgus had a much higher prevalence of lateral lesions than limbs that were in the most varus group (29.5% vs. 8.6%; $P = 0.002$ for alignment and lateral lesions). When we subdivided the 45 valgus limbs at the median for valgus angulation (3 degrees), we found that the most valgus limbs had a higher prevalence of lateral lesions (40.9%) than less valgus limbs (26.1%).

Of 223 knees followed, 39 showed evidence of medial progression. Of 75 knees with medial lesions, 27 (36.0%) showed medial progression compared with 12 of 148 knees (8.1%) without medial lesions (**Table 3**), a 6.5-fold increase in the odds of progression. Of the knees with medial progression, 27 (69.2%) had medial bone marrow lesions at baseline.

We found a similar strong association between lateral lesions and lateral progression (**Table 3**). Of 40 knees with lateral lesions, 10 (25.0%) showed lateral progression compared with 10 of 183 without lateral lesions (5.5%). Of knees with lateral progression, half (10 of 20) had lateral bone marrow lesions at baseline. The odds of lateral progression were increased approximately sixfold among knees with lateral lesions.

While medial lesions increased the risk for medial progression, they decreased the risk for lateral progression (**Table 4**). Specifically, only 3 of 75 knees with medial lesions (4.0%) showed lateral progression compared with 17 of 148 knees without these lesions (11.5%). Lateral lesions had a modest protective effect on medial progression; 5 of 40 knees with lateral lesions showed such progression (12.5%) versus 34 of 183 knees without lateral lesions (18.6%). When we examined only patients who had alignment evaluations, this association with progression increased to an odds ratio of 8.9, which was attenuated by 37% (from 8.9 to 5.6) after adjustment for alignment (**Table 5**). For the association of lateral bone marrow edema with progression, the association was attenuated 53% by adjustment for alignment and became statistically nonsignificant. When we analyzed lesions by the bone involved, we found similar effects. For example, medial lesions, whether in the tibia or femur, increased the risk for medial progression. Also, when we looked at knees with lesions in only medial or lateral locations, not in both, we found similar results.

DISCUSSION

Results of this longitudinal study to examine the effects of bone marrow edema on the course of knee osteoarthritis suggest that these lesions powerfully predict risk for local structural deterioration. Risk for medial progression was increased more than sixfold in patients with medial lesions, and patients with lateral lesions were at a commensurate high risk for lateral progression. That medial lesions protected against lateral progression suggests a uniquely local effect.

Another important finding was that bone marrow lesions are strongly related to frontal plane malalignment. Varus limbs in our study had an extraordinarily high prevalence of medial bone marrow lesions, whereas lateral lesions occurred preferentially in valgus limbs. Indeed, much of the relationship of bone marrow edema lesions to radiographic progression was explained by their association with malalignment. While malalignment and bone marrow lesions are closely correlated, each adds prognostic information in the presence of the other. For example, according to **Table 5**, in the presence of bone marrow edema, every 3-degree departure from neutral alignment increases the odds of progression on the same side as the malalignment

Table 4. **Bone Marrow Edema Lesions and Their Relation to Contralateral Radiographic Progression**

Variable	Knees with Progression on Opposite Side of Lesion for All Patients in the Longitudinal Analysis, *n/n (%)*	Adjusted Odds Ratio (95% CI)*
Lateral progression		
Medial lesion	3/75 (4.0)	0.3 (0.1–1.0)
No medial lesion	17/148 (11.5)	1
Medial progression		
Lateral lesion	5/40 (12.5)	0.7 (0.2–1.8)
No lateral lesion	34/183 (18.6)	1

* Adjusted for age, sex, and body mass index. Odds ratios (95% CI) for these variables were as follows for lateral and medial progression, respectively: age (per year), 1.1 (1.0–1.1) and 1.0 (0.9–1.0); sex (women), 3.1 (1.1–8.7) and 0.7 (0.4–1.6); body mass index (per unit), 1.0 (0.9–1.1) and 1.1 (1.0–1.1).

by 50% to 100%. Disease progression in patients with bone marrow lesions may be the consequence of the lesions themselves, or malalignment may produce both the traumatic bone lesions and the wearing away of local cartilage evidenced by joint space loss.

Even after adjustment for malalignment, there was a substantial residual association of bone marrow edema lesions with radiographic progression. Alignment as assessed on long-limb radiographs represents alignment during standing, or so-called static alignment. Dynamic alignment or alignment during walking as measured in a gait laboratory can differ from static alignment (22, 23). Knees with medial lesions in which static alignment was neutral could have dynamic malalignment. If that were true, it would suggest that frontal plane malalignment statically or dynamically accounts for the preponderance of structural progression in knee osteoarthritis.

On histopathologic examination, bone marrow edema lesions show surprisingly little edema (24, 25) but show abnormal bone with excessive fibrosis, small areas of osteonecrosis, and extensive bony remodeling with reversal lines. Such remodeling often occurs after fatigue fractures in bone, although microfractures themselves have not been reported. The picture is most consistent with ongoing bone trauma, which would help explain the association of malalignment with these lesions and would be consistent with histologic findings in states in which bone marrow edema occurs with microfractures.

Although bone marrow edema was a powerful predictor of disease progression in our study, that does not mean that MRIs should be ordered to evaluate these lesions in patients with knee osteoarthritis. Currently, there are no treatments for bone marrow edema. Furthermore, it is not clear whether these lesions directly cause structural damage or are a consequence of malalignment. It remains to be determined whether adding MRIs to identify bone marrow edema, long-limb radiographs to check alignment, or both to the evaluation of knee osteoarthritis adds sufficient predictive information to merit their clinical use.

Table 5. **Bone Marrow Edema Lesions and Their Relation to Progression before and after Adjustment for Mechanical Alignment***

Variable	Adjusted Odds Ratio (95% CI)†	Adjusted Odds Ratio† Including Alignment (95% CI)‡
Medial lesion	8.9 (3.6–21.8)	5.6 (2.1–14.8)
No medial lesion	1 (referent)	1
Lateral lesion	5.9 (1.9–18.1)	2.8 (0.8–10.1)
No lateral lesion	1 (referent)	1

* Analyses restricted to 183 knees with limb alignment measurement and longitudinal follow-up.
† Adjusted for age, sex, and body mass index. Odds ratios (95% CI) for these variables were as follows for medial progression before and after adjustment for alignment, respectively: age (per year), 1.0 (0.9–1.0) and 1.0 (0.9–1.0); sex (women), 1.0 (0.4–2.4) and 1.2 (0.5–2.9); body mass index (per unit), 1.1 (1.0–1.2) and 1.1 (1.0–1.2); alignment (per degree), 1.1 (1.0–1.3). Odds ratios (95% CI) for these variables were as follows for lateral progression before and after adjustment for alignment, respectively: age (per year), 1.0 (0.9–1.0) and 1.1 (1.0–1.1); sex (women), 4.2 (1.3–14.1) and 3.0 (0.8–11.1); body mass index (per unit), 0.9 (0.8–1.1) and 1.0 (0.9–1.1); alignment (per degree), 0.8 (0.7–0.9).
‡ Alignment was treated as a continuous measure in these analyses.

Limitations of our study include chronologic assessment of alignment in the middle of the study rather than at the beginning. We found the same relations among malalignment, marrow edema, and progression (although fewer patients progressed) when we restricted analyses to knees from the middle to the end of the study. Also, our study was based in the Veterans Health Care System and therefore included mostly men, while most persons with knee osteoarthritis are women. Last, we found that the contralateral side of the joint was protected from progression. However, since we evaluated progression by radiography, we could have missed contralateral cartilage loss that might have been more sensitively detected by MRI.

Further studies evaluating the longitudinal course of bone marrow edema lesions are needed. Better understanding of the interrelation of cartilage and the bone immediately under it is also necessary. Our findings have major implications for the design of clinical studies, including trials in osteoarthritis. They suggest that patients at high risk for progression could be efficiently identified by screening for bone marrow edema on MRI. Indeed, 69.2% of knees that eventually developed medial progression in our study had large medial lesions at baseline. Our definition of bone marrow edema lesions excluded smaller lesions. However, when such lesions were included, we found that 81% of knees with medial progression had had medial lesions. Until now, it has been extraordinarily difficult to detect structural deterioration, and this has prevented the development of preventive therapies. In fact, in longitudinal radiograph-based studies of knee osteoarthritis (26, 27), most patients did not show progression, especially if followed for less than 5 years. Bone marrow edema could be used to select patients at truly high risk for structural progression. Trials restricted to such patients would provide a sample that includes many persons likely to experience progression and would facilitate the development of preventive treatments.

In summary, in patients with knee osteoarthritis, bone marrow edema lesions in bone underneath cartilage markedly increase risk for structural progression in the knee, especially in the compartment affected by the bone marrow lesion. Bone marrow edema lesions are strongly related to malalignment toward the side of the lesion. Our findings provide fundamental insights into the process of structural deterioration in knee osteoarthritis.

From Boston University and the Veterans Affairs Boston Health Care System, Boston, Massachusetts; and University of Rochester, Rochester, New York.

Acknowledgments: The authors thank field staff and study participants for generously giving their time. They also thank Dr. Kenneth Pritzker for valuable discussions on the pathology of bone marrow edema.

Grant Support: By the National Institutes of Health (AR47785) and by an Arthritis Foundation Clinical Sciences Grant.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: David T. Felson, MD, MPH, Boston University School of Medicine, 715 Albany Street, A203, Boston, MA 02118.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, et al.** The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health. 1994;84:351-8. [PMID: 8129049]

2. **Mazzuca S, Brandt K.** The utility of scintigraphy in explaining x-ray changes and symptoms of knee osteoarthritis [Abstract]. Presented at 46th Annual Orthopaedic Research Society Meetings, Orlando, Florida, 12–15 March 2000.

3. **Dieppe P, Cushnaghan J, Young P, Kirwan J.** Prediction of the progression of joint space narrowing in osteoarthritis of the knee by bone scintigraphy. Ann Rheum Dis. 1993;52:557-63. [PMID: 8215615]

4. **Hutton CW, Higgs ER, Jackson PC, Watt I, Dieppe PA.** 99mTc HMDP bone scanning in generalised nodal osteoarthritis. II. The four hour bone scan image predicts radiographic change. Ann Rheum Dis. 1986;45:622-6. [PMID: 3740991]

5. **Brandt KD, Mazzuca SA, Conrozier T, Dacre JE, Peterfy CG, Provvedini D, et al.** Which is the best radiographic protocol for a clinical trial of a structure modifying drug in patients with knee osteoarthritis? J Rheumatol. 2002;29:1308-20. [PMID: 12064851]

6. **Boegard T, Rudling O, Dahlstrom J, Dirksen H, Petersson IF, Jonsson K.** Bone scintigraphy in chronic knee pain: comparison with magnetic resonance imaging. Ann Rheum Dis. 1999;58:20-6. [PMID: 10343536]

7. **McAlindon TE, Watt I, McCrae F, Goddard P, Dieppe PA.** Magnetic resonance imaging in osteoarthritis of the knee: correlation with radiographic and scintigraphic findings. Ann Rheum Dis. 1991;50:14-9. [PMID: 1994861]

8. **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. 2001;134:541-9. [PMID: 11281736]

9. **Rangger C, Kathrein A, Freund MC, Klestil T, Kreczy A.** Bone bruise of the knee: histology and cryosections in 5 cases. Acta Orthop Scand. 1998;69:291-4. [PMID: 9703406]

10. **Lazzarini KM, Troiano RN, Smith RC.** Can running cause the appearance of marrow edema on MR images of the foot and ankle? Radiology. 1997;202:540-2. [PMID: 9015087]

11. **Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD.** The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA. 2001;286:188-95. [PMID: 11448282]

12. **Buckland-Wright JC, Macfarlane DG, Lynch JA, Jasani MK, Bradshaw CR.** Joint space width measures cartilage thickness in osteoarthritis of the knee: high resolution plain film and double contrast macroradiographic investigation. Ann Rheum Dis. 1995;54:263-8. [PMID: 7763102]

13. **Mazzuca SA, Brandt KD, Katz BP.** Is conventional radiography suitable for evaluation of a disease-modifying drug in patients with knee osteoarthritis? Osteoarthritis Cartilage. 1997;5:217-26. [PMID: 9404466]

14. **Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al.** Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986;29:1039-49. [PMID: 3741515]

15. **Moreland JR, Bassett LW, Hanker GJ.** Radiographic analysis of the axial alignment of the lower extremity. J Bone Joint Surg Am. 1987;69:745-9. [PMID: 3597474]

16. **Buckland-Wright JC, Bird CF, Ritter-Hrncirik CA, Cline GA, Tonkin C, Hangartner TN, et al.** X-ray technologists' reproducibility from automated measurements of the medial tibiofemoral joint space width in knee osteoarthritis for a multicenter, multinational clinical trial. J Rheumatol. 2003;30:329-38. [PMID: 12563691]

17. **Buckland-Wright C.** Protocols for precise radio-anatomical positioning of the tibiofemoral and patellofemoral compartments of the knee. Osteoarthritis Cartilage. 1995;3 Suppl A:71-80. [PMID: 8581753]

18. **Altman RD, Hochberg M, Murphy WA Jr, Wolfe F, Lequesne M.** Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage. 1995;3 Suppl A:3-70. [PMID: 8581752]

19. **LaValley MP, Felson DT.** Statistical presentation and analysis of ordered categorical outcome data in rheumatology journals. Arthritis Rheum. 2002;47:255-9. [PMID: 12115154]

20. **Zhang Y, Glynn RJ, Felson DT.** Musculoskeletal disease research: should we analyze the joint or the person? J Rheumatol. 1996;23:1130-4. [PMID: 8823682]

21. **Rothman KJ.** Using regression models in epidemiologic analysis. In: Rothman KJ. Epidemiology: An Introduction. New York: Oxford Univ Pr; 2002:181-97.

22. **Andriacchi TP.** Dynamics of knee malalignment. Orthop Clin North Am. 1994;25:395-403. [PMID: 8028883]

23. **Johnson F, Leitl S, Waugh W.** The distribution of load across the knee. A comparison of static and dynamic measurements. J Bone Joint Surg Br. 1980;62:346-9. [PMID: 7410467]

24. **Zanetti M, Bruder E, Romero J, Hodler J.** Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. Radiology. 2000;215:835-40. [PMID: 10831707]

25. **Bergman AG, Willen HK, Lindstrand AL, Pettersson HT.** Osteoarthritis of the knee: correlation of subchondral MR signal abnormalities with histopathologic and radiographic features. Skeletal Radiol. 1994;23:445-8. [PMID: 7992110]

26. **Ledingham J, Regan M, Jones A, Doherty M.** Factors affecting radiographic progression of knee osteoarthritis. Ann Rheum Dis. 1995;54:53-8. [PMID: 7880123]

27. **Schouten JS, van den Ouweland FA, Valkenburg HA.** A 12 year follow up study in the general population on prognostic factors of cartilage loss in osteoarthritis of the knee. Ann Rheum Dis. 1992;51:932-7. [PMID: 1417116]

Current Author Addresses: Drs. Felson, LaValley, and Hill and Ms. McLaughlin, Ms. Goggins, and Ms. Li: Boston University School of Medicine, 715 Albany Street, A203, Boston, MA 02118.
Drs. M.E. Gale and D. Gale: Radiology Department, Veterans Affairs Boston Health Care System, 150 Huntington Avenue, Boston, MA 02130.
Dr. Totterman: Department of Radiology, University of Rochester Medical Center, 601 Elmwood Avenue, PO Box 694, Rochester, NY 14624-8648.

Author Contributions: Conception and design: D.T. Felson.
Analysis and interpretation of the data: D.T. Felson, J. Goggins, M.P. LaValley, S. Totterman, W. Li.
Drafting of the article: D.T. Felson.
Critical revision of the article for important intellectual content: M.P. LaValley, C. Hill, D. Gale.
Final approval of the article: D.T. Felson.
Provision of study materials or patients: D.T. Felson, J. Goggins.
Statistical expertise: D.T. Felson, M.P. LaValley.
Obtaining of funding: D.T. Felson.
Administrative, technical, or logistic support: D.T. Felson, J. Goggins, M.P. LaValley, M.E. Gale, W. Li, D. Gale.
Collection and assembly of data: D.T. Felson, S. McLaughlin.