Osteoarthritis and Cartilage (2010) **18,** 47–53

doi:10.1016/j.joca.2009.08.018

Osteoarthritis and Cartilage

Subchondral bone marrow lesions are highly associated with, and predict subchondral bone attrition longitudinally: the MOST study

F. W. Roemer†‡*, T. Neogi§, M. C. Nevitt‖, D. T. Felson§, Y. Zhu§, Y. Zhang§, J. A. Lynch‖, M. K. Javaid‖¶, M. D. Crema†, J. Torner#, C. E. Lewis†† and A. Guermazi†

† *Quantitative Imaging Center (QIC), Department of Radiology, Boston University Medical Center, Boston, MA, USA*

‡ *Department of Radiology, Klinikum Augsburg, Augsburg, Germany*

§ *Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, USA*

‖ *Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA*

¶ *Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, UK*

Department of Epidemiology at the University of Iowa, Iowa City, IA, USA

†† *Division of Preventive Medicine, University of Alabama, Birmingham, AL, USA*

Summary

Objective: Subchondral bone attrition (SBA) is defined as flattening or depression of the osseous articular surface. The causes of attrition are unknown, but remodeling processes due to chronic overload that are reflected as bone marrow edema-like lesions (BMLs) on magnetic resonance imaging (MRI) might predispose the subchondral bone to subsequent attrition. The aim of this study was to evaluate the cross-sectional and longitudinal association of BMLs with SBA in the same subregion of the knee.

Design: The Multicenter Osteoarthritis (MOST) study is a longitudinal observational study of individuals who have or are at high risk for knee osteoarthritis. Subjects with available baseline and 30-months follow-up MRI were included. Patients with a recent history of trauma or findings suggestive of post-traumatic bone marrow changes were excluded. Subchondral BMLs and SBA were scored semiquantitatively from 0 to 3 in 10 tibiofemoral subregions. We evaluated the association of prevalent BMLs at baseline with the presence of prevalent and incident SBA on a per-subregion basis using logistic regression. We also cross-sectionally evaluated the association of BML grade severity and presence of baseline SBA.

Results: One thousand and twenty-five knees were included. 8.9% of the analyzed knee subregions showed SBA present at baseline and 9.2% of subregions exhibited prevalent subchondral BMLs. The adjusted odds ratio (OR) for prevalent SBA for subregions with prevalent BMLs was 18.8 [95% confidence intervals (CI) 15.9–22.4]. A larger BML size was directly associated with an increased risk of prevalent SBA. 195 (2.2%) subregions exhibited incident SBA at follow-up. The adjusted OR for incident SBA was 5.3 [95% CI 3.6–7.7] when compared to subregions without BMLs as the reference.

Conclusions: Prevalent and incident SBA is strongly associated with subchondral BMLs in the same subregion. One explanation for the presence and development of SBA is subchondral remodeling due to increased stress, which is reflected as BMLs on MRI.

Key words: Attrition, Magnetic resonance imaging, Osteoarthritis, Knee, Bone, Bone marrow lesions.

Introduction

Osteoarthritis (OA) is the most prevalent joint disease and is increasingly common in the aging Western society[1,2]. Although, traditionally considered to be a disease of the hyaline articular cartilage, OA is a process of the whole joint including cartilage, bone and intra- and periarticular structures[3–7]. Of these joint tissues, the subchondral bone probably plays an important role for the development and progression of OA[8–11]. Increased subchondral bone turnover as measured by scintigraphy has been observed far in advance of any radiographic changes of OA and predicted subsequent radiographic changes of OA[12]. Also a number of animal studies have shown that damage to the subchondral bone through loading may lead to cartilage damage[13–15]. Other experimental animal models demonstrate subchondral bone changes very early after induction of disease[16,17]. Subchondral bone attrition (SBA) is defined on radiographs or magnetic resonance imaging (MRI) as flattening or depression of the articular surface unrelated to gross fracture[18,19]. On MRI, the assessment of bone attrition is usually performed using the Whole-Organ Magnetic Resonance Imaging Score (WORMS)[20]. Flattening or depression of the articular surfaces is graded based on the subjective degree of deviation from the normal contour on multiple tomographic images. As in radiographs, reading these deviations on MRIs is not simple, which is the reason why Reichenbach *et al.* suggested to use a conservative

*Address correspondence and reprint requests to: Frank Roemer, Department of Radiology, Boston University Medical Center, FGH Building, 3rd floor, 820 Harrison Avenue, Boston, MA 02118, USA. Tel: 1-617-414-3893; Fax: 1-617-638-6616; E-mail: froemer@bu.edu

Received 22 May 2009; revision accepted 24 August 2009.

definition of attrition in order to detect "true" attrition on MRI[19].

An association of radiographically and MRI-detected SBA with pain has been reported by different research groups[18,21,22]. Recent MRI-based studies have shown that SBA is present also in a relevant number of knees with early and even pre-radiographic OA[19]. Also presence of SBA predicts adjacent progressive cartilage loss longitudinally and is strongly associated with malalignment within the same compartment[23,24].

As it is unknown what causes SBA in OA, one explanation could be subchondral remodeling processes and microfractures due to chronic overload that are reflected as subchondral bone marrow lesions (BMLs) on MRI[3,4]. A recent cross-sectional population-based study reported that in more than 70% of all knees, both maximal SBA score and maximal bone marrow lesion (BML) score coexisted in the same knee region[18].

The causes of these remodeling processes could be overlying cartilage defects or other features that might increase mechanical subchondral stress such as meniscal damage and malalignment[4,10,25]. Histologically, despite exhibiting normal bone tissue, BMLs seem to consist of a mixture of tissues that reflect chronic as well as active remodeling processes[26–28]. The alteration of the osseous surface contour could be a result of these subchondral remodeling processes including necrosis, fibrosis and focal osseous collapse[26,28]. As subchondral bone marrow lesions are a non-specific finding on MRI and represent a multitude of differential diagnoses such as traumatic bone contusions and fractures with or without disruption of the articular surface, osteonecrosis, inflammation, idiopathic BMLs, and others, in this study only typical OA-related BMLs were assessed defined according to the literature[26,29].

Thus, the aim of our study was to investigate whether subchondral BMLs are associated with prevalent SBA and whether BMLs in the same subregion of the knee precede SBA in the same subregion longitudinally using two different definitions of MRI-detected SBA as previously suggested[19].

Patients and methods

STUDY DESIGN AND SUBJECTS

Subjects were participants in The Multicenter Osteoarthritis (MOST) study, a prospective epidemiological study of 3026 persons aged 50–79 years with a goal of identifying risk factors for incident and progressive knee OA in a sample either with OA or at high risk of developing disease. Those considered at high risk included persons who were overweight or obese, those with knee pain, aching or stiffness on most of the last 30 days, a history of knee injury that made it difficult to walk for at least 1 week, or previous knee surgery.

Subjects were recruited from two US communities, Birmingham, Alabama and Iowa City, Iowa through mass mailing of letters and study brochures, supplemented by media and community outreach campaigns. The study protocol was approved by the Institutional Review Boards at the University of Iowa, University of Alabama, Birmingham, University of California, San Francisco and Boston University Medical Campus.

Subjects were excluded from MOST if they screened positive for rheumatoid arthritis[30], had ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, had renal insufficiency that required hemo- or peritoneal dialysis, a history of cancer (except for non-melanoma skin cancer), had or planned to have bilateral knee replacement surgery, were unable to walk without assistance, or were planning to move out of the area in the next 3 years.

In the present study we included all participants with available baseline and 30-months follow-up MRI. These knees had been selected for MRI assessment for one or more of three substudies of MOST that were defined in the original grant proposal: (1) a cohort study of risk factors for radiographic OA progression consisting of randomly selected knees with either patellofemoral or tibiofemoral (TF) OA; (2) a case-control study of risk factors for incident radiographic OA; and (3) a case-control study of risk factors for new onset of consistent frequent knee pain[31]. Altogether 1025 subjects were selected for MRI reading and were included in the present study.

RADIOGRAPHS

At baseline, all subjects underwent weight-bearing posteroanterior (PA) fixed flexion knee radiographs using the protocol by Peterfy *et al.* and a plexiglass positioning frame (SynaFlexer™)[32]. A musculoskeletal radiologist and a rheumatologist experienced in reading study films, both blinded to case/control status and clinical data, graded all PA X-rays according to the Kellgren–Lawrence (KL) scale. Radiographic TF OA was considered present if KL grade ≥ 2. If readers disagreed on the presence of radiographic OA, the film readings were adjudicated by a panel of three readers.

MRI ACQUISITION

MRIs were obtained in both knees with a 1.0 T dedicated MRI system (OrthOne™, ONI Medical Systems, Wilmington, MA) with a circumferential extremity coil using fat-suppressed (fs) fast spin-echo proton density-weighted (PDw) sequences in two planes, sagittal repetition time (TR) = 4800 ms, echo time (TE) = 35 ms, 3 mm slice thickness, 0 mm interslice gap, 32 slices, 288×192 matrix, two excitations number of acquisitions (NEX), 140×140 mm field of view (FOV), echo train length (ETL) = 8) and axial (TR = 4680 ms, TE = 13 ms, 3 mm slice thickness, 0 mm interslice gap, 20 slices, 288×192 matrix, two NEX, 140×140 mm FOV, ETL = 8) and a short tau inversion-recovery (STIR) sequence in the coronal plane (TR = 6650 ms, TE = 15 ms, TI = 100 ms, 3 mm slice thickness, 0 mm interslice gap, 28 slices, 256×192 matrix, two NEX, 140 mm^2 FOV, ETL = 8).

MRI INTERPRETATION

Two musculoskeletal radiologists, with 6 and 8 years experience in standardized semiquantitative MR assessment of knee OA, blinded to radiographic OA grade, study hypotheses, and clinical data, read BMLs and SBA according to the WORMS method[20]. Baseline and follow-up MRIs were read paired and with the chronological order known to the readers. BMLs and SBA were scored in each of the five subregions in the medial and lateral compartments, for a total of 10 subregions per knee. BML size was scored from 0–3 based on the extent of regional involvement (0 = none; 1 = <25% of the subregion, 2 = 25–50% of the subregion; 3 = >50% of the subregion). BMLs were defined as ill-delineated areas of hyperintensity directly adjacent to the subchondral plate on the STIR and fs PDw images. Knees that showed typical radiologic signs of traumatic bone contusions, osteonecrosis, fracture or malignant bone infiltration were excluded from the analysis. However, of all analyzed MRIs only one knee showed a subacute tibial depression fracture at follow-up and was excluded. Bone attrition was scored from 0 to 3 based on the subjective degree of deviation from the normal contour: 0 = normal, 1 = mild, 2 = moderate and 3 = severe. The weighted kappa coefficients of inter-observer reliability (performed on 30 knees read by both readers) for the readings of BMLs (comparing 0–3 scores in each subregion) and SBA (also comparing 0–3 scores in each subregion) were 0.64 and 0.63 respectively.

Knees that showed typical radiologic signs of traumatic bone contusions, osteonecrosis, fracture or malignant bone infiltration were excluded from the analysis. However, of all analyzed MRIs only one knee showed a subacute tibial depression fracture at follow-up and was excluded.

ANALYTIC APPROACH

We evaluated the association of prevalent BMLs (score > 0) at baseline with the presence of prevalent and incident SBA (score > 0) in the *same subregion* across knees using logistic regression adjusting for age, gender, body mass index (BMI), ethnicity and radiographic OA. Subregions without SBA (SBA = 0) at baseline that developed SBA (SBA > 0) at the follow-up visit were defined as incident SBA. Subregions without subchondral BMLs at baseline were defined as the reference group for the analysis. The correlation among SBA in different subregions in the same knee was adjusted by generalized estimation equation model. Analyses were also performed to evaluate the association between different baseline BML grades and presence of SBA. In addition, we performed a sensitivity analysis by defining prevalent SBA as all subregions with SBA baseline scores of ≥ 2 and incident SBA as subregions with baseline SBA scores of 0 or 1, and ≥ 2 at the follow-up visit ("strict" SBA definition). All statistical calculations were performed using SAS® software (Version 9.1 for Windows; SAS Institute; Cary, NC).

Results

One thousand and twenty-five participants were included (1 knee per subject). Their mean age (standard deviation) (SD) was 63 years (8), with a mean BMI (SD) of 30.3 (5.1). Sixty-four per cent were female. The average interval

from baseline to the follow-up visit was 939 days, with a range of 827−1622 days. Of the 1025 knees studied, 51% had TF radiographic knee OA at baseline (KL grade ≥ 2). At baseline, 24.5% of knees were graded as K/L 2, 22.2% as K/L 3 and 4.5% as K/L 4. At the 30-months follow-up visit the proportion of K/L 1 knees had decreased by about half and the number of K/L 4 knees had more than doubled. Three hundred and ninety eight (38.8%) of the subjects complained about knee symptoms on most days in the past 30 days prior to the baseline visit. At the follow-up this number had slightly increased. Varus malalignment was present in 510 (50.4%) and valgus malalignment in 201 (19.9%) of the knees at the baseline visit. The detailed demographic data are presented in Table I.

Ten thousand two hundred and forty seven subregions were assessable at the baseline visit. Nine hundred and nine (8.9%) knee subregions showed SBA present at baseline. Using the strict definition of SBA, 289 (2.8%) of subregions showed SBA at baseline and 945 (9.2%) of knee subregions exhibited prevalent subchondral BMLs with the majority of these ($n = 667/6.5\%$) being grade 1 lesions. Grade 2 BMLs were observed in 181 (1.8%) and grade 3 lesions in 97 (1.0%) of subregions. Of the subregions without SBA (SBA = 0) at baseline ($n = 8699$), incident attrition was observed in 195 (2.2%) subregions. Of the 9267 subregions showing no attrition at baseline (SBA = 0 or 1) 108 (1.2%) exhibited incident attrition using the strict SBA definition (Table II).

A strong association between prevalent BMLs and presence of SBA in the same subregion was observed cross-sectionally (Table III). The larger the BML was the higher was the association observed. The association was comparable for both SBA definitions. In the adjusted model, baseline presence of BMLs (grade > 0) in a subregion was associated with a 5.3 times higher odds (95% confidence intervals (CI) 3.6−7.7, $P < 0.001$) of developing SBA in the corresponding subregion across all knees over 30 months when compared to a subregion without any BML at baseline (Fig. 1). When using a stricter definition for the development of "definite" SBA (grade ≥ 2) within a subregion and considering grades 0 and 1 as "no attrition", the corresponding odds ratio (OR) was 10.4 (95% CI 7.0−15.6, $P < 0.001$) (Fig. 2). Larger size of baseline BMLs was associated with higher odds of incident SBA at follow-up using the "strict" incident SBA definition, but not for the first definition (Tables IV and V). However, using that definition only one subregion with a grade 3 BML at baseline showed incident SBA at follow-up.

Table I
Demographic characteristics

Participant characteristics at baseline	$N = 1025$
Mean age [SD; range]	62.9 [7.9; 50−79]
Female [%]	660 [64.4]
Mean BMI [SD; range], kg/m2	30.3 [5.1; 18.0−55.8]
Ethnicity: Caucasian [%]	882 [86.0]
TF radiographic osteoarthritis [%]	525 [51.2]
Kellgren & Lawrence grade [%]	
0	326 [31.9]
1	173 [16.9]
2	251 [24.5]
3	227 [22.2]
4	46 [4.5]
Knee symptoms on most days in the past 30 days [%]	398 [38.8]
Malalignment [%]	
Varus	510 [50.4]
Neutral	301 [29.7]
Valgus	201 [19.9]
Follow-up time [SD; range], days	939 [73; 827−1622]
Participant characteristics at follow-up	**$N = 1025$**
Kellgren & Lawrence grade [%]	
0	279 [27.3]
1	98 [9.6]
2	258 [25.2]
3	294 [28.7]
4	94 [9.2]
Knee symptoms on most days in the past 30 days [%]	429 [41.9]

Discussion

In this study, we found that presence of MRI-detected subchondral BMLs was highly associated with SBA in the same subregion cross-sectionally. Further, prevalent BMLs predicted development of attrition in the same subregion across knees over 30 months. This association could be confirmed also for a stricter definition of SBA as concerns had been raised that SBA might easily be "overread" on MRI[19].

These findings suggest that BMLs, which are a reflection of increased subchondral metabolism and remodeling[26], might lead in some cases to alterations in the subchondral osseous plate and eventually weakening and deformity of the osseous articular contour. BMLs are thought to be a reflection of compartment-specific load most probably due to malalignment[3,4]. As malalignment leads to altered stress in a joint, subchondral bone remodeling with resultant attrition can occur at those areas of increased stress in response to loads and in response to local microfractures as a result of those loads[33]. The MRI feature of a subchondral BML then may be regarded as an intermediate of increased stress in

Table II
Baseline bone marrow lesions and attrition status

Subregional attrition or BML status	Subregions *n*/*N* (%)
Prevalent BML among knee subregions at baseline (%)	
Any	945/10,247 (9.2)
Grade 1	667/10,247 (6.5)
Grade 2	181/10,247 (1.8)
Grade 3	97/10,247 (1.0)
Prevalent bone attrition among knee subregions at baseline (%)	
Defined as grades ≥1	909/10,247 (8.9)
Defined as grades ≥2	289/10,247 (2.8)
Incident bone attrition among knee subregions at follow-up (%)	
Defined as SBA grades ≥1 at follow-up, and 0 at baseline	195/8699* (2.2)
Defined as SBA grades ≥2 at follow-up, and 0 or 1 at baseline	108/9267*,† (1.2)

BML − bone marrow lesion.

*Numbers of subregions between baseline and follow-up differ for the two definitions. For the incidence analysis only those subregions were included that were readable at baseline and follow-up.

†More subregions are eligible for this definition as all subregions without prevalent SBA were included (including grades 0 and 1 for this definition) at baseline.

Table III
Presence of bone marrow lesions and prevalent bone attrition in the same subregion

BML status in subregion	Subregions with prevalent SBA *n*/*N* (%)	Crude model OR (95% CI)	Model adjusting age, sex, BMI, race, TF radiographic OA OR (95% CI) *P*-value
Absent	397/9301 (4.3)	1.0 (reference)	1.0 (reference)
Present (any BML)	512/944 (54.2)	26.6 [22.6, 31.3]	18.8 [15.9, 22.4] <0.0001*
BML grade			
0	397/9301 (4.3)	1.0 (reference)	1.0 (reference)
1	316/666 (47.5)	20.2 [16.9, 24.3]	14.3 [11.8, 17.3] <0.0001*
2	121/181 (66.9)	45.2 [32.7, 62.6]	34.3 [24.0, 49.0] <0.0001*
3	75/97 (77.3)	76.5 [47.0, 124.3]	49.8 [29.8, 83.1] <0.0001*
P-value for linear trend			<0.0001*

BML – bone marrow lesion.
*Statistically significant, defined as $P < 0.05$.

this subregion, which may lead to attrition in later stages. Radin *et al.* described in an animal model of OA based on repetitive impulsive loading an increase in subchondral bone formation and a decrease in porosity, which has been associated with relative stiffening of bone. Horizontal splitting and deep fibrillation of the overlying articular cartilage followed these early bone changes[14,15]. These theories seem to be supported by recent work by Neogi *et al.* who showed that malalignment is associated with SBA in a compartment-specific manner, suggesting that SBA may

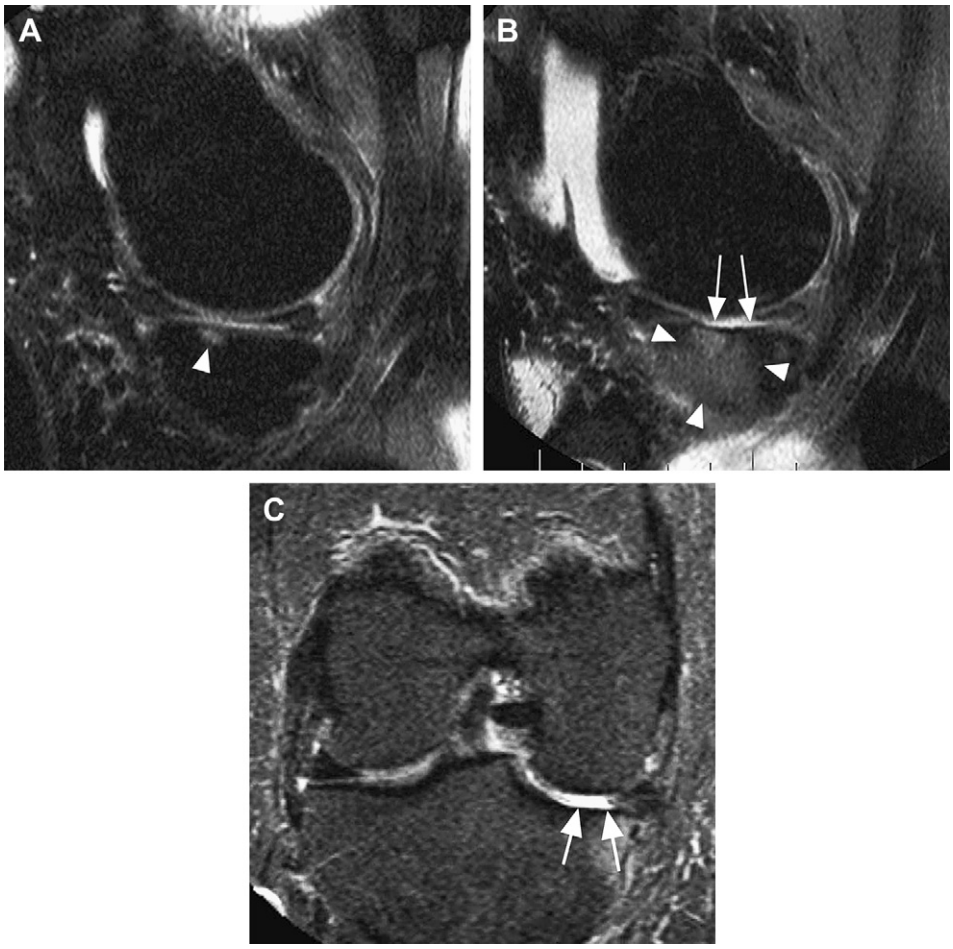

Fig. 1. Incident SBA in the medial TF compartment. (A). Sagittal fs PDw MRI at baseline depicts bone marrow lesion in the central subregion of the medial tibial plateau (arrowhead). No attrition is observed. (B). Sagittal fs PDw MRI at 30-months follow-up, demonstrates incident grade 2 attrition in the central subregion of the medial tibial plateau (arrows). Bone marrow lesion has progressed markedly in size (arrowheads). (C). Corresponding coronal STIR MRI also shows attrition, visualized as depression of the medial tibial plateau (arrows).

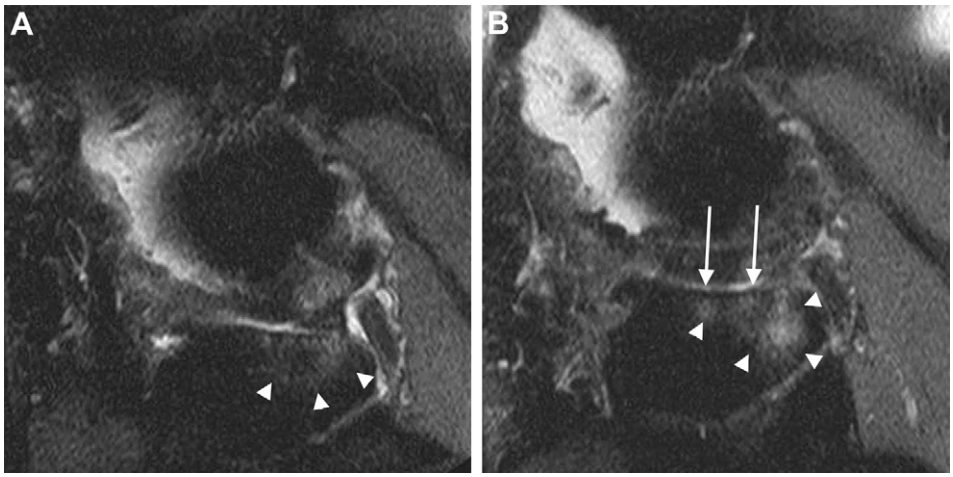

Fig. 2. Incident SBA in the lateral tibia. (A). Sagittal fs PDw MRI at baseline shows subchondral bone marrow lesion in the central and posterior subregions of the lateral tibial plateau (arrowheads). (B). Sagittal fs PDw MRI at 30-months follow-up shows incident attrition in the central subregion of the lateral tibial plateau. Also note progressive adjacent subchondral bone marrow lesion (arrowheads).

be a reflection of local mechanical load experienced through the knee joint[24]. The same group also demonstrated that baseline presence of SBA is strongly associated with adjacent cartilage loss over time occurring within the same subregion of a given knee. These results were consistent for both compartments of the knee, although the effects were of greater magnitude in specific subregions that experience greater loading[23]. Thus the co-occurrence of SBA, malalignment, cartilage loss and presence of BMLs within the same subregions of a knee, particularly for subregions thought to experience greater loading, seems to suggest that abnormal mechanical loading may be the common cause of these pathologies.

Depending on the definition, we found prevalent SBA in about 9% of the knee subregions, and using the strict definition in about 3% of subregions. Subchondral BMLs were seen in about 9% of the subregions with most of these being small lesions, which is a comparable number to the data presented by Roemer *et al.* in a recent publication from the MOST study[8]. In our study cohort incident attrition was observed in about 2% of subregions and in 1% if the strict definition was applied. Hernandez-Molina *et al.* reported a prevalence of bone attrition (MRI defined as grades ≥ 2) in 28% of the knees with pain and in 10% of knees without pain[18]. A subregional analysis concerning SBA prevalence was not performed in that study. Reichenbach *et al.* reported data from the Framingham study, where SBA prevalence was strongly associated with disease severity. In that study, MRI-detected SBA was present in about 14% of the knees with KL grade 0 and 100% in knees with a KL grade of 4[19].

There was a strong association between prevalent BMLs and SBA that increased with BML size. One might argue that this association only reflects disease severity as BMLs and attrition are thought to be more prevalent in advanced stages of OA[4,19]. However, the strong spatial association of subchondral BMLs and attrition directly adjacent to each other suggests otherwise.

There are potential limitations to the current study. First, reader bias for finding SBA whenever a BML is present, and *vice versa*, cannot be ruled out completely. This is a general limitation of studies that examine associations among radiological features on the same image, as readers cannot be blinded to the presence of other features as both features are depicted in the identical images and thus are seen simultaneously. Readers were unaware of the study

Table IV
Baseline bone marrow lesions and incident bone attrition (defined as any grade ≥ 1)

BML status in subregion	Subregions with incident SBA *n*/*N* (%)	Crude model OR (95% CI)	Model adjusting age, sex, BMI, race, TF radiographic OA OR (95% CI) *P*-value
Absent	156/8298 (1.9)	1.0	1.0 (reference)
Present (any BML)	39/401 (9.7)	5.6 (3.9, 8.1)	5.3 (3.6, 7.7) $<0.0001^*$
Absent	156/8298 (1.9)	1.0	1.0 (reference)
Grade 1	34/326 (10.4)	6.1 (4.1, 9.0)	5.7 (3.8, 8.5) $<0.0001^*$
Grade 2	4/56 (7.1)	4.0 (1.4, 11.2)	3.7 (1.3, 10.4) 0.01^*
Grade 3	1/19(5.3)	2.9 (0.4, 21.9)	2.7 (0.4, 20.1) 0.34
P-value for linear trend			$<0.0001^*$

BML – bone marrow lesion.
*Statistically significant, defined as $P < 0.05$.

Table V
Baseline bone marrow lesions and incident bone attrition (using "strict" definition: SBA defined as any grade ≥ 2)

BML status in subregion	Subregions with incident SBA *n*/*N* (%)	Crude model OR (95% CI)	Model adjusting age, sex, BMI, race, TF radiographic OA OR (95% CI) *P*-value
Absent	54/8590 (0.6)	1.0	1.0 (reference)
Present (any BML)	54/677 (8.0)	13.7 (9.3, 20.2)	10.4 (7.0, 15.6) <0.0001*
Absent	54/8590 (0.6)	1.0	1.0 (reference)
Grade 1	35/517(6.8)	11.5 (8.4, 17.7)	8.9 (5.7, 13.9) <0.0001*
Grade 2	8/112 (7.1)	12.2 (5.6, 26.2)	9.4 (4.3, 20.4) <0.0001*
Grade 3	11/48 (22.9)	47.0 (22.8, 97.0)	31.8 (15.1, 67.1) <0.0001*
P-value for linear trend			<0.0001*

BML – bone marrow lesion.
*Statistically significant, defined as $P < 0.05$.

hypothesis, which makes reading bias unlikely. Secondly, our study results are limited to the TF joint only. There is no validated reading of bone attrition in the femoropatellar joint, and we therefore limited our investigations to the TF joint. We did not correlate the MRI findings with X-ray readings concerning attrition but a moderate to strong correlation between MRIs and radiographs for bone attrition of the TF joint has been shown previously[19]. We did not look at BML status at follow-up as we used BMLs only as a baseline predictor for subsequent SBA. It has been shown previously that subchondral BMLs are a highly variable feature of OA with possible progression, regression and also resolution over the course of the disease[8]. It would be interesting to analyze if BMLs that predicted attrition always progressed as shown in the examples in Figs. 1 and 2 or if there are subregions with regressing or resolving BMLs exhibiting incident SBA. However, such an analysis was not the focus of the present study. There were too few subregions with incident SBA defined as grade ≥1 to evaluate the dose response relationship across the full range of BML size at baseline.

We did not analyze if clinical findings are associated with the MRI changes of the subchondral bone. However, this was not focus of the present study and would have gone beyond the scope of our work. Several groups have previously shown that subchondral BMLs seem to play an important role in explaining pain and bone attrition seems also to be independently associated with knee symptoms[18,31,34]. Additional studies are needed to further elucidate if incident attrition is independently associated with onset of knee symptoms.

Subchondral BMLs exhibit typical signal characteristics on MRI and are common but non-specific findings. BMLs may be observed in conjunction with trauma, chronic cartilage damage and OA, as an idiopathic entity or as a concomitant feature of other pathologies such as osteonecrosis, inflammation or tumor[35–40]. In this context especially post-traumatic marrow pathologies have to be mentioned as these are common and traumatic bone contusions or subchondral fractures may easily be misinterpreted as chronic or OA-related BMLs. Several studies have used similar terminology and have shown different clinical outcomes depending on the extent and nature of these traumatic alterations[41–44]. We excluded traumatic BMLs by participants' history and whenever typical traumatic MRI findings we observed[29,45–47]. The latter was found in one knee, which was excluded from the analysis.

In summary, we demonstrated that presence of subchondral bone marrow lesions is highly associated with concomitant bone attrition in the same subregions across knees. Further, subchondral BMLs are a strong predictor of future development of attrition when compared to regions without baseline BMLs. These findings suggest that subchondral remodeling processes, which are reflected on MRI as BMLs, predispose that articular region to weakening of the subchondral osseous plate, which eventually will be detectable as a deformity or depression of the osseous articular contour. The common pathogenetic mechanism of both processes might be increased loading due to malalignment or damage to other protective joint structures such as the menisci or an intact articular chondral surface.

Conflict of interest

Ali Guermazi is president of Boston Imaging Core Lab, LLC (BICL), Boston, MA, a company providing radiological image assessment services. He is shareholder of Synarc, Inc.

Frank Roemer and Michel Crema are shareholders of BICL.

None of the other authors have declared any possible conflict of interest.

Acknowledgments

We would like to thank the participants and staff of the MOST study at the clinical sites in Birmingham, AL and Iowa City, IA and at the Coordinating Center at University of California San Francisco, San Francisco, CA.
The MOST study is supported by National Institutes of Health (NIH) grants from the National Institute on Aging to Drs Lewis (U01-AG-18947), Torner (U01-AG-18832), Nevitt (U01-AG-19069), and Felson (U01-AG-18820).

References

1. Arthritis prevalence and activity limitations – United States, 1990. MMWR Morb Mortal Wkly Rep 1994;43:433–8.
2. Prevalence of disabilities and associated health conditions among adults – United States, 1999. MMWR Morb Mortal Wkly Rep 2001; 50:120–5.
3. 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 2003;139:330–6.

4. Hunter DJ, Zhang Y, Niu J, Goggins J, Amin S, LaValley MP, *et al*. Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. Arthritis Rheum 2006;54:1529–35.
5. Guermazi A, Zaim S, Taouli B, Miaux Y, Peterfy CG, Genant HK. MR findings in knee osteoarthritis. Eur Radiol 2003;13:1370–86.
6. Pelletier JP, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. Arthritis Rheum 2001;44:1237–47.
7. Amin S, Guermazi A, Lavalley MP, Niu J, Clancy M, Hunter DJ, *et al*. Complete anterior cruciate ligament tear and the risk for cartilage loss and progression of symptoms in men and women with knee osteoarthritis. Osteoarthritis Cartilage 2008;16:897–902.
8. Roemer FW, Guermazi A, Javaid MK, Lynch JA, Niu J, Zhang Y, *et al*. Change in MRI-detected subchondral bone marrow lesions is associated with cartilage loss – the MOST study a longitudinal multicenter study of knee osteoarthritis. Ann Rheum Dis 2009;68:1461–5.
9. Dedrick DK, Goldstein SA, Brandt KD, O'Connor BL, Goulet RW, Albrecht M. A longitudinal study of subchondral plate and trabecular bone in cruciate-deficient dogs with osteoarthritis followed up for 54 months. Arthritis Rheum 1993;36:1460–7.
10. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Abram F, Choquette D, Haraoui B, *et al*. Correlation between bone lesion changes and cartilage volume loss in patients with osteoarthritis of the knee as assessed by quantitative magnetic resonance imaging over a 24-month period. Ann Rheum Dis 2008;67:683–8.
11. Hunter DJ, Gerstenfeld L, Bishop G, Davis AD, Mason ZD, Einhorn TA, *et al*. Bone marrow lesions from osteoarthritis knees are characterized by sclerotic bone that is less well mineralized. Arthritis Res Ther 2009; 11:R11.
12. 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.
13. Carlson CS, Loeser RF, Jayo MJ, Weaver DS, Adams MR, Jerome CP. Osteoarthritis in cynomolgus macaques: a primate model of naturally occurring disease. J Orthop Res 1994;12:331–9.
14. Radin EL, Martin RB, Burr DB, Caterson B, Boyd RD, Goodwin C. Effects of mechanical loading on the tissues of the rabbit knee. J Orthop Res 1984;2:221–34.
15. Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. Clin Orthop Relat Res 1986;34–40.
16. Anderson-MacKenzie JM, Quasnichka HL, Starr RL, Lewis EJ, Billingham ME, Bailey AJ. Fundamental subchondral bone changes in spontaneous knee osteoarthritis. Int J Biochem Cell Biol 2005;37: 224–36.
17. Hayami T, Pickarski M, Zhuo Y, Wesolowski GA, Rodan GA, Duong le T. Characterization of articular cartilage and subchondral bone changes in the rat anterior cruciate ligament transection and meniscectomized models of osteoarthritis. Bone 2006;38:234–43.
18. Hernandez-Molina G, Neogi T, Hunter DJ, Niu J, Guermazi A, Roemer FW, *et al*. The association of bone attrition with knee pain and other MRI features of osteoarthritis. Ann Rheum Dis 2008;67:43–7.
19. Reichenbach S, Guermazi A, Niu J, Neogi T, Hunter DJ, Roemer FW, *et al*. Prevalence of bone attrition on knee radiographs and MRI in a community-based cohort. Osteoarthritis Cartilage 2008 Sep;16: 1005–10.
20. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, *et al*. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage 2004;12:177–90.
21. Juni P, Reichenbach S, Dieppe P. Osteoarthritis: rational approach to treating the individual. Best Pract Res Clin Rheumatol 2006;20:721–40.
22. Torres L, Dunlop DD, Peterfy C, Guermazi A, Prasad P, Hayes KW, *et al*. The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. Osteoarthritis Cartilage 2006; 14:1033–40.
23. Neogi T, Zhang Y, Niu J, Lynch J, Nevitt MC, Guermazi A, *et al*. Cartilage loss occurs in the same subregions as subchondral bone attrition: the MOST study. Arthritis Rheum 2008;58:S235.
24. Neogi T, Nevitt MC, Niu J, Sharma L, Roemer F, Guermazi A, *et al*. Subchondral bone attrition is a reflection of compartment-specific mechanical load: the MOST study. Ann Rheum Dis 2009 Sep 17 [Epub ahead of print].
25. Sharma L, Eckstein F, Song J, Guermazi A, Prasad P, Kapoor D, *et al*. Relationship of meniscal damage, meniscal extrusion, malalignment, and joint laxity to subsequent cartilage loss in osteoarthritic knees. Arthritis Rheum 2008;58:1716–26.
26. 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.
27. Martig S, Boisclair J, Konar M, Spreng D, Lang J. MRI characteristics and histology of bone marrow lesions in dogs with experimentally induced osteoarthritis. Vet Radiol Ultrasound 2007;48:105–12.
28. 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.
29. Roemer FW, Frobell R, Hunter DJ, Crema MD, Fischer W, Bohndorf K, *et al*. MRI-detected subchondral bone marrow signal alterations of the knee joint: terminology, imaging appearance, relevance and radiological differential diagnosis. Osteoarthritis Cartilage 2009;17:1115–31.
30. Karlson EW, Sanchez-Guerrero J, Wright EA, Lew RA, Daltroy LH, Katz JN, *et al*. A connective tissue disease screening questionnaire for population studies. Ann Epidemiol 1995;5:297–302.
31. Felson DT, Niu J, Guermazi A, Roemer FW, Aliabadi P, Clancy M, *et al*. The development of knee pain correlates with enlarging bone marrow lesions on MRI. Arthritis Rheum 2007;56:2986–92.
32. Peterfy CG, Guermazi A, Zaim PF. Non-fluoroscopic method for flexed radiography of the knee that allows reproducible joint-space width measurement. Arthritis Rheum 1998;41:S361.
33. Burr DB. The importance of subchondral bone in the progression of osteoarthritis. J Rheumatol Suppl 2004;70:77–80.
34. 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.
35. Vellet AD, Marks PH, Fowler PJ, Munro TG. Occult posttraumatic osteochondral lesions of the knee: prevalence, classification, and short-term sequelae evaluated with MR imaging. Radiology 1991;178:271–6.
36. Yamamoto T, Bullough PG. Spontaneous osteonecrosis of the knee: the result of subchondral insufficiency fracture. J Bone Joint Surg Am 2000;82:858–66.
37. Frobell RB, Roos HP, Roos EM, Hellio Le Graverand MP, Buck R, Tamez-Pena J, *et al*. The acutely ACL injured knee assessed by MRI: are large volume traumatic bone marrow lesions a sign of severe compression injury? Osteoarthritis Cartilage 2008;16:829–36.
38. Korompilias AV, Karantanas AH, Lykissas MG, Beris AE. Bone marrow edema syndrome. Skeletal Radiol 2009;38:425–36.
39. Moosikasuwan JB, Miller TT, Math K, Schultz E. Shifting bone marrow edema of the knee. Skeletal Radiol 2004;33:380–5.
40. Lee SK, Suh KJ, Kim YW, Ryeom HK, Kim YS, Lee JM, *et al*. Septic arthritis versus transient synovitis at MR imaging: preliminary assessment with signal intensity alterations in bone marrow. Radiology 1999;211:459–65.
41. Lahm A, Spank H, Mrosek E, Frauendorf H, Merk H. Relevance of different sequences in MRI-detected subchondral bone damage of the knee joint and possible therapeutic options. Sportverletz Sportschaden 2008;22:38–44.
42. Boks SS, Vroegindeweij D, Koes BW, Bernsen RM, Hunink MG, Bierma-Zeinstra SM. Clinical consequences of posttraumatic bone bruise in the knee. Am J Sports Med 2007;35:990–5.
43. Frobell RB, Le Graverand MP, Buck R, Roos EM, Roos HP, Tamez-Pena J, *et al*. The acutely ACL injured knee assessed by MRI: changes in joint fluid, bone marrow lesions, and cartilage during the first year. Osteoarthritis Cartilage 2009;17:161–7.
44. Vincken PW, Ter Braak BP, van Erkel AR, Coerkamp EG, Mallens WM, Bloem JL. Clinical consequences of bone bruise around the knee. Eur Radiol 2006;16:97–107.
45. Sanders TG, Medynski MA, Feller JF, Lawhorn KW. Bone contusion patterns of the knee at MR imaging: footprint of the mechanism of injury. Radiographics 2000;20:S135–51.
46. Palmer WE. Magnetic resonance imaging of knee trauma: biomechanical approach. Top Magn Reson Imaging 2003;14:161–78.
47. Yu JS, Cook PA. Magnetic resonance imaging (MRI) of the knee: a pattern approach for evaluating bone marrow edema. Crit Rev Diagn Imaging 1996;37:261–303.