Frequency of Bone Marrow Lesions and Association with Pain Severity: Results from a Population-based Symptomatic Knee Cohort

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ABSTRACT. ***Objective.*** To evaluate the prevalence of bone marrow lesions (BML) and their association with pain severity in a population-based cohort of symptomatic early knee osteoarthritis (OA).

Methods. Subjects with knee pain (n = 255), age 40–79 years, were evaluated by radiograph and magnetic resonance imaging (MRI) and classified into OA stages: no OA (NOA), preradiographic OA (PROA), and radiographic OA (ROA). BML were graded 0–3 (none, mild, moderate, severe) in 6 regions and defined as (1) BMLsum = the sum of 6 scores; and (2) BMLmax = the worst score at any region. Pain was assessed by the Western Ontario and McMaster Universities OA Index (WOMAC). Linear regression analysis was completed to assess the association of Total WOMAC Pain (primary outcome) versus BMLsum or BMLmax. Secondary outcomes were WOMAC Pain on Walking and WOMAC Pain on Climbing Stairs. All analyses were adjusted for age, sex, body mass index, OA stage, joint effusion, and meniscal damage.

Results. BML were present in 11% of NOA, 38% of PROA, and 71% of ROA subjects ($p < 0.001$). No association was seen for BMLsum or BMLmax versus Total WOMAC Pain or Pain on Walking. However, BMLsum was associated with Pain on Climbing Stairs [regression coefficients (RC) = 0.09, 95% CI 0.00–0.18]. BMLmax was associated with Pain on Climbing Stairs, with the strongest association for severe BML (RC 0.60, 95% CI 0.04–1.17).

Conclusion. BML were present in 38% of PROA and 71% of ROA subjects in this symptomatic knee cohort. BML were significantly associated with Pain on Climbing Stairs but not Total WOMAC or Pain on Walking. (J Rheumatol First Release March 1 2011; doi:10.3899/jrheum.100587)

Key Indexing Terms:
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Knee osteoarthritis (OA) is the most common type of knee arthritis, affecting 10% of subjects age 63 years or older[1], with many developing severe disability, often requiring arthroplasty and incurring significant treatment costs[2].

Magnetic resonance imaging (MRI) is the "gold standard" for noninvasive assessment of joint structures in OA[3], but in clinical practice, the diagnosis of OA usually stems from characteristic symptoms, the physical examination, and radiographic findings. When MRI is used, a common finding in patients with OA is bone marrow lesions

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(BML)[4,5,6,7,8,9,10,11]. While the pathophysiology of this MRI finding remains uncertain, several cross-sectional studies have suggested that BML are associated with the presence[4,6,7,8] or severity[5] of knee pain. Four of these studies[4,5,6,7] involved subjects with radiographic OA (ROA) while the remaining study[8] used an older cohort of healthy subjects (aged 50–79 yrs). In addition, 3 longitudinal studies have evaluated the association of pain with BML. Felson, *et al*[9] showed that an increase in BML after a 15-month period was significantly associated with incident knee pain. In contrast, 2 other longitudinal studies did not show an association between BML and pain severity[10,11]. Phan, *et al*[10] suggested that the small sample size (n = 40) and the development of pain tolerance led to their results. Kornaat, *et al*[11] proposed that because their subjects had familial ROA in multiple joints, the pathogenesis of knee pain in these subjects may be substantially different from that in subjects with primary knee OA.

From these studies, the association of pain with BML is not clear. In addition, little is known about the prevalence of BML in earlier stages of disease and whether pain severity is associated with BML across the spectrum of OA. We examined the association of BML with pain severity in a population-based study of symptomatic subjects, the majority of whom had preradiographic OA (PROA).

MATERIALS AND METHODS

The study population has been described[12]. Invitations were mailed to randomly selected households in the Lower Mainland of Vancouver, British Columbia. This was followed by standardized telephone screening, and eligible subjects were then evaluated by clinical examination. Inclusion criteria were (1) age 40–79 years; (2) pain, aching, or discomfort in or around the knee on most days of the month at any time in the past; and (3) pain, aching, or discomfort in or around the knee during the past 12 months. Exclusion criteria were (1) inflammatory arthritis or fibromyalgia; (2) knee arthroplasty; (3) knee injury or surgery within the past 6 months; (4) knee pain referred from the hips or back based on clinical examination; and (5) inability to undergo MRI. For subjects with bilateral knee pain, the more symptomatic knee was chosen as the study knee.

Imaging and OA stage classification. Subjects were evaluated by radiography and MRI of the study knee, as described[12]. Briefly, knee radiographs were obtained using a fixed-flexion technique with the SynaFlexer positioning frame[13] and a skyline view in the supine position. Radiographs were scored blinded by 2 independent readers using the Kellgren-Lawrence (KL) 0–4 grading. The interrater reliability for KL grade was high, with an intraclass correlation coefficient (ICC) of 0.79. Differences in readings were adjudicated by consensus.

MRI was performed on a GE 1.5-T magnet using a transmitter-receiver extremity knee coil. The imaging protocol included 4 MRI sequences: (1) fat-saturated T1-weighted 3-D spoiled gradient-echo sequence with images obtained in the sagittal plane with reformat images in the axial and coronal planes [repetition time (TR) 52 ms, time to echo (TE) 10 ms, flip angle 60˚, field of view (FOV) 12 cm, matrix 256 × 128, section thickness 1–1.5 mm with 1 signal averaged]; (2) fat-saturated T2-weighted fast spin-echo (FSE) sequence with images obtained in the coronal plane (TR 3000 ms, TE 54 ms, echo train length of 8, FOV 14 cm, matrix 256 × 192, section thickness 4 mm, with an intersection gap of 1 mm with 2 signals averaged); (3) T1-weighted FSE sequence with images obtained in the oblique sagittal plane (TR 450 ms, TE minimum full, echo train length 2, band width 20 Hx/pixel, FOV 16 cm, matrix 384 × 224, section thickness 4 mm, intersection gap 1 mm with 2 signals averaged; and (4) T2-weighted FSE sequence with images obtained in the oblique sagittal plane (TR 4025 ms, TE 102 ms, echo train length 17, band width 20 Hx/pixel, FOV 16 cm, matrix 320 × 288, section thickness 3 mm, intersection gap 0 mm with 4 signals averaged).

Six joint sites were assessed by MRI: lateral femoral condyle, lateral tibial plateau, medial femoral condyle, medial tibial plateau, patella, and trochlear groove. Cartilage was graded on a 0–4 semiquantitative scale based on the following definitions, described by Disler, *et al*[14]: 0 = normal; 1 = abnormal signal without a cartilage contour defect; 2 = contour defect of < 50% cartilage thickness; 3 = contour defect of 50%–99% cartilage thickness; and 4 = 100% cartilage contour defect with subjacent bone signal abnormality. If multiple defects were present at a given site, the score was based on the worst defect. MRI was read by a single reader blinded to radiograph and clinical information. Intrareader reliability of cartilage readings was high, ranging from 0.84 to 1.0 for different cartilage surfaces.

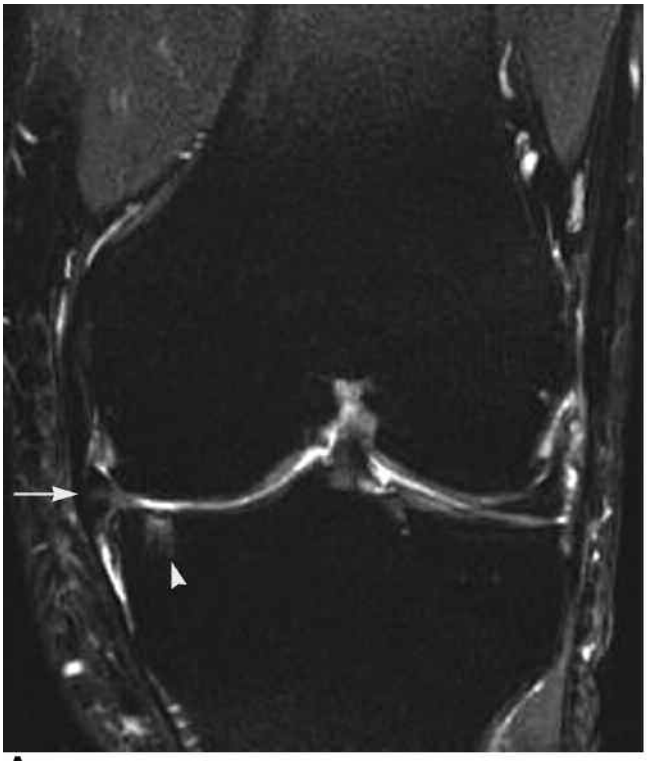
Based on radiograph and MR cartilage (MRC) scores (using the worst cartilage lesion to determine the MRC score), subjects were classified into 3 subgroups: No OA (NOA; KL < 2 and MRC < 2), PROA (KL < 2 and MRC ≥ 2), and ROA (KL ≥ 2 and MRC ≥ 2).

BML were scored on a scale of 0–3 (0 = none, 0% of site; 1 = mild, < 25% of site; 2 = moderate, 25%–49% of site; and 3 = severe, ≥ 50% of the site) at 6 knee sites: lateral femoral condyle, lateral tibial plateau, medial femoral condyle, medial tibial plateau, patella, and trochlear groove. Examples of BML grading are shown in Figure 1. If multiple BML were present at a given site, the score was based on the worst BML. ICC for intrarater reliability of BML readings ranged from 0.81 to 0.93 for different joint sites, with the exception of patellar BML, where the ICC was 0.58. BMLsum was defined as the sum of the BML score from each site of the knee (sum of 6 scores). BMLmax was defined as the highest score of any of the 6 sites of the knee.

Pain assessment. Pain was determined by the Western Ontario and McMaster Universities OA Index (WOMAC), Version 3.1, a valid and standardized questionnaire commonly used for the assessment of OA[15]. This index determines pain severity through 5 questions: pain when walking on a flat surface (Pain on Walking), pain going up or down stairs (Pain on Climbing Stairs), pain at night while in bed, pain sitting or lying, and pain when standing upright[15]. The study knee was specified on the WOMAC questionnaire. Subjects were instructed to think of the study knee only when completing the WOMAC questions. Each question was scored on a 100-mm visual analog scale (VAS; 100 = most severe pain)[15]. Total WOMAC Pain was defined as the sum of these 5 questions (normalized to a 0–100 scale, 100 = most severe pain). Pain was also described by frequency and duration of knee pain. Frequency of knee pain was defined as the number of days within a 30-day month that a subject experienced pain, while duration of pain was defined as the number of years that a subject experienced pain.

Statistical analysis. Data were summarized by OA groups using frequencies and medians (with range of minimum and maximum values) as appropriate. Data between OA groups were compared using the Kruskal-Wallis test, the Pearson chi-squared test, or/and the Cochran-Armitage test for trend, as appropriate. Statistical significance was set at $p < 0.05$. All analyses incorporated stratum sampling weights.

Our objective was to determine the association of BML and pain severity. Our primary outcome was Total WOMAC Pain (dependent variable). We hypothesized that because activity-induced pain is a common symptom of OA in its earlier stages (e.g., PROA), Total WOMAC Pain may not be the ideal measurement; therefore, we chose Pain on Walking and Pain on Climbing Stairs as secondary outcomes. BMLsum was chosen *a priori* as the primary predictor of interest since intuitively it is more representative of the burden of BML of the entire knee. We were also interested in the association of BMLmax with pain and whether the definition of BML would have an effect on our study results since both BMLmax[4,5,6,7,8] and BMLsum[9,11] have been used in previous studies.



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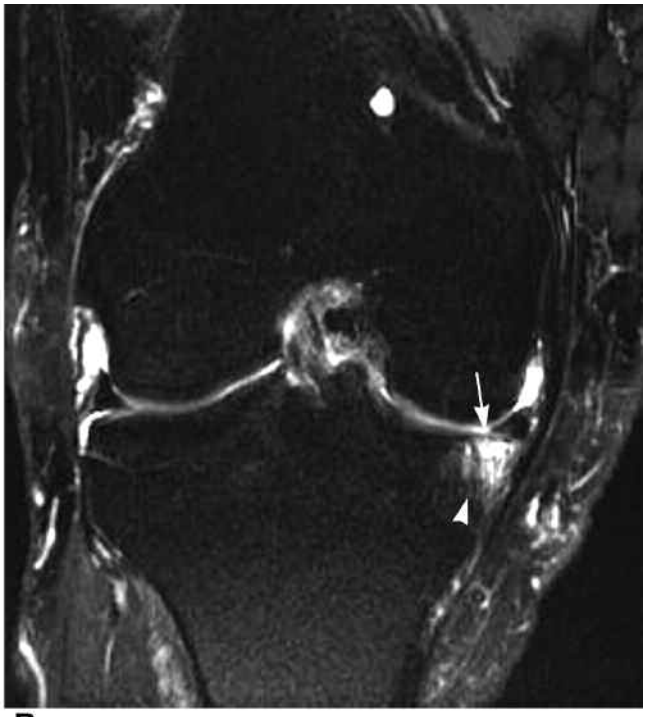

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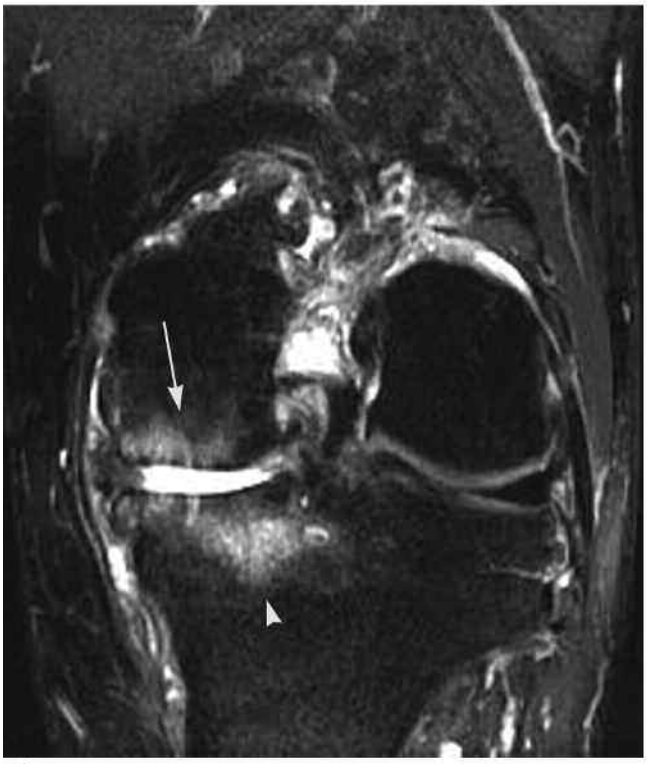

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Figure 1. A. Coronal fat-suppressed T2-weighted MRI shows a grade 1 bone marrow lesion (BML) of the medial tibial plateau (arrowhead). There is diffuse cartilage loss of the medial tibial plateau and femoral condyle. The body of the medial meniscus is partially macerated and extruded (arrow). B. Coronal fat-suppressed T2-weighted MRI shows a grade 2 BML of the medial tibial plateau (arrowhead). There is focal cartilage loss of the medial tibial plateau (arrow). C. Coronal fat-suppressed T2-weighted MRI shows a grade 3 BML of the medial tibial plateau (arrowhead) and weight-bearing femoral condyle (arrow). There is diffuse cartilage loss of the medial tibial plateau and femoral condyle. The body of the medial meniscus is partially macerated and extruded.

Univariate linear regression models were developed for BMLsum or BMLmax (independent variables) versus Total WOMAC Pain, Pain on Walking, or Pain on Climbing Stairs (dependent variables) (i.e., BMLsum vs Total WOMAC Pain, BMLmax vs Total WOMAC Pain, etc.). Models with BMLsum were also fit with a quadratic term (BMLsumSq) to allow for nonlinearity. The residuals from the models with untransformed dependent variables (i.e., Total WOMAC Pain, Pain on Walking, or Pain on Climbing Stairs) did not follow a normal distribution. As a result, we applied a natural logarithmic transformation. Regression coefficients (RC) were determined and denoted changes of logarithmic pain units per unit of

BML. Statistical significance was set at $p < 0.05$. Analyses were adjusted for age, sex, body mass index (BMI), OA stage, joint effusion, and meniscal damage.

RESULTS

The study included 255 subjects, of which 33 (13%) had NOA, 124 (49%) had PROA, and 98 (38%) had ROA (Table 1). The ROA group had the highest median age and median BMI ($p < 0.001$ and $p = 0.014$, respectively) followed by the PROA group and then the NOA group. Sex was not statistically different between groups ($p = 0.924$).

Median BMLsum and BMLmax were significantly different between OA groups ($p < 0.001$ for both), with a trend of increasing severity of BMLmax with increasing OA stage. BML (BMLmax > 0) were present in 11% of NOA, 38% of PROA, and 71% of ROA subjects ($p < 0.001$), weighted for stratum sampling. Total WOMAC Pain, Pain on Walking, and Pain on Climbing Stairs also differed significantly among OA groups ($p = 0.001$, $p = 0.001$, and $p = 0.005$, respectively). Duration and frequency of knee pain were highest in the ROA groups, with significant differences seen between OA groups ($p < 0.001$ for both).

Table 2 shows the linear regression analysis results for BMLsum or BMLmax versus Total WOMAC Pain, Pain on Walking, or Pain on Climbing Stairs. Results were similar unadjusted (data not shown) and adjusted for age, sex, BMI, OA stage, joint effusion, and meniscal damage. Women were found to experience more pain (data not shown), in keeping with previous studies[16,17,18,19].

There was no association of BMLsum or BMLmax with Total WOMAC Pain or Pain on Walking (Table 2), although the association of BMLsum with Pain on Walking was borderline statistically significant. However, BMLsum was associated with Pain on Climbing Stairs (RC 0.09, 95% CI 0.00–0.18). For this association, the 95% CI was fairly wide and bordered on unity. BMLmax was also associated with Pain on Climbing Stairs (Table 2). Although the strongest association was observed for severe BML (i.e., BMLmax = 3: RC 0.60, 95% CI 0.04–1.17), there was no clear dose-response relationship for BMLmax with Pain on Climbing Stairs.

DISCUSSION

In our population-based, cross-sectional study of subjects with knee pain, which consisted predominantly of PROA subjects, we found that BML were highly prevalent, affecting 71% of subjects with ROA and 38% of subjects with PROA. We found significant associations of BMLsum with Pain on Climbing Stairs but not with Total WOMAC Pain or Pain on Walking. We also found that BMLmax was associated with Pain on Climbing Stairs. Thus BMLsum, which reveals the burden of BML of the whole joint, is likely a better predictor of activity-related pain given that there was also a trend toward significance for the association of BMLsum with Pain on Walking.

The prevalence of BML in subjects with symptomatic ROA has previously been reported to be 77.5%[4] and 73%[20]. Our prevalence of 71% in ROA is in keeping with those studies. In our study, we further extend those findings to the symptomatic PROA stage of disease, where we found a prevalence of BML of 38%, a novel finding for this subcohort of early-stage disease.

The finding of no association of BML (both BMLmax and BMLsum) with Total WOMAC Pain is of interest. Although the WOMAC is a standard outcome measure in OA, the pain scale includes pain at night and pain while sitting, which likely identifies pain severity related to more advanced stages of OA. Given that our study population consisted of a majority of PROA, the WOMAC Pain scale

Table 1. Descriptive results of OA groups (sample-weighted).

	NOA, n = 33	PROA, n = 124	ROA, n = 98	p*
Median age, yrs (range)	47.3 (40.1–79.9)	53.8 (39.8–79.3)	62.2 (45.2–79.8)	< 0.001
Sex (% women)	58	55	57	0.924**
Median BMI (range), kg/m^2	24.1 (18.1–33.3)	24.6 (18.7–41.3)	26.5 (19.3–49.6)	0.014
Median BMLsum (range)	0.0 (0–3)	0.0 (0–5)	2.0 (0–10)	< 0.001
BMLmax > 0, %	11	38	71	< 0.001**
BMLmax = 0, %	89	62	29	< 0.001†
BMLmax = 1, %	7	19	31	< 0.001†
BMLmax = 2, %	0	15	28	< 0.001†
BMLmax = 3, %	3	4	13	< 0.001†
Median duration of knee pain, yrs (range)	4.1 (0.7–3.0)	5.0 (0–45)	12.2 (0–65)	< 0.001
Median frequency of knee pain, no. days/mo (range)	20.0 (0–30)	25.0 (0–30)	30.0 (0–30)	0.001
Median total WOMAC pain (range)	19.0 (0–26.0)	12.0 (0–77.0)	21.0 (0–74.8)	0.001
Median Pain on Walking (range)	5.0 (0–61.0)	5.0 (0–98.0)	16.0 (0–96.0)	0.001
Median Pain on Climbing Stairs (range)	18.0 (0–100)	25.0 (0–100)	37.0 (0–96.0)	0.005

*Kruskal-Wallis test unless otherwise indicated. **Pearson chi-squared test. †Pearson chi-squared and Cochrane-Armitage trend tests. OA: osteoarthritis; NOA: no OA; PROA: preradiographic OA; ROA: radiographc OA; BMI: body mass index; BMLsum: sum of 6 bone marrow lesion scores; BMLmax: worst BML score at any region; WOMAC: Western Ontario and McMaster Universities OA Index.

Table 2. Adjusted regression coefficients (95% CI) for bone marrow lesion (BML) pain severity*. Significant results shown in bold type ($p < 0.05$).

	Primary Outcome	Secondary Outcomes	
	Total WOMAC Pain	Pain on Walking	Pain on Climbing Stairs
BMLsum	0.05 (–0.04, 0.14)	0.11 (–0.01, 0.21)	**0.09 (0.00, 0.18)**
BMLmax = 0**	0	0	0
BMLmax = 1	0.20 (–0.18, 0.58)	0.02 (–0.46, 0.50)	**0.40 (0.02, 0.79)**
BMLmax = 2	0.17 (–0.23, 0.57)	0.19 (–0.30, 0.69)	0.35 (–0.06, 0.75)
BMLmax = 3	0.45 (–0.11, 1.01)	0.54 (–0.13, 1.20)	**0.60 (0.04, 1.17)**

*Regression coefficients were adjusted for age, sex, BMI, OA stage, joint effusion, and meniscal damage. **Regression coefficients for BMLmax = 1–3 were normalized to BMLmax = 0 set at 0. BML: bone marrow lesion; WOMAC: Western Ontario and McMaster Universities OA Index; BMLsum: sum of 6 bone marrow lesion scores; BMLmax: worst BML score at any region; BMI: body mass index.

may not be an optimal outcome measure. This is supported by Creamer, *et al*[21], who reported that pain on sitting or pain at night had different associations from pain on walking or pain on climbing stairs. They concluded that different pain scales measure different facets of the pain experience in knee OA and therefore cannot be used interchangeably[21].

We had hypothesized that activity-induced pain, namely WOMAC Pain on Walking and Pain on Climbing Stairs, might demonstrate stronger associations with BML in this population of early knee OA. BMLsum was indeed associated with severity of activity-induced pain, specifically Pain on Climbing Stairs, although the 95% CI was fairly wide. This finding is not entirely consistent with previous cross-sectional studies of knee OA[4,5,6,7,8] and may relate to differences in definitions of pain/BML or to the fact that most studies were performed in ROA subjects. Felson, *et al*[4] showed that in ROA subjects, the presence of BML was associated with knee pain, with a stronger association seen for larger BML. Similarly, in a population of middle-aged women (age 32–56 yrs), Hayes, *et al*[6] demonstrated that in subjects with ROA, large BML (> 10 mm) were seen significantly more frequently in those with pain compared to those without pain; however, no association was seen for symptomatic subjects with normal radiographs or for small BML (< 10 mm). In a recent study of ROA subjects, Lo and colleagues[7] reported that maximal BML was significantly associated with prevalent weight-bearing pain (pain on walking, climbing stairs, or standing), but not with non-weight-bearing pain (pain at night or lying down). Zhai, *et al*[8] completed a population-based study of healthy subjects aged 50–79 years that included 52% of asymptomatic subjects, and reported that BML were significant predictors of prevalent knee pain. While these studies support a link between BML and the presence of knee pain, few studies have evaluated whether BML are associated with pain severity. In a subgroup analysis, Zhai, *et al*[8] reported that pain severity was associated with increased BMI and hip joint-space narrowing, but not BML of the knee. Torres, *et al*[5] found that BML score in the worst compartment was associated with pain severity in ROA where pain was measured on a single 0–100 VAS. Our study is the first to show an association of BML with WOMAC weight-bearing pain severity in a symptomatic study population that spans the full spectrum of disease.

It is of interest that previous cross-sectional studies have evaluated maximal BML scores[4,5,6,7,8], rather than the sum of BML within the joint. Two longitudinal studies have used BMLsum[9,11]. In our study, BMLsum was more consistently associated with activity-induced pain severity compared to BMLmax. The ideal definition of BML requires further investigation and may depend on the study question.

Our study was limited by its cross-sectional design and hence no causal relationship between BML and pain can be inferred. In addition, we studied the association of pain severity with BML of the entire knee. Therefore, compartmental differences in BML and their associations with pain severity or location of pain within the knee were not examined. Our study was also limited by the fact that multiple joint structures (e.g., tendon/ligament pathology, synovitis, and subchondral bone pathology) may potentially contribute to knee pain. In particular, the involvement of subchondral bone pathology has been associated with knee pain in OA[5,22,23,24,25] and may be related to BML[26,27]. In a recent longitudinal study of subjects at risk of developing OA or having OA, Crema, *et al*[26] found that prevalent BML were strongly associated with subchondral cyst-like lesions in the same subregion of the knee. In the same population, Roemer, *et al*[27] found that prevalent and incident subchondral bone attrition was also associated with BML in the same subregion. Together, these findings may support the bone contusion theory in which subchondral remodeling (e.g., cyst-like lesions and bone attrition) may be caused by increased mechanical stress, which may be demonstrated as BML on MRI[26,27]. Further, subchondral sclerosis has also been linked to knee pain in OA[6,28]. In a population of middle-aged women with ROA, Hayes, *et al*[6] found that subchondral sclerosis (< 5 mm and > 5 mm) was more frequent in those with pain compared to those without pain. In a cross-sectional study of 167 subjects with ROA, Szebenyi, *et al*[28] reported that of 3 radiological findings including

osteophytes, joint-space narrowing, and subchondral sclerosis, the latter showed the strongest association with knee pain. Although BML were the main focus of our study, we did examine the prevalence of subchondral sclerosis (data not included). We found that BML were more prevalent than subchondral sclerosis, particularly in the PROA and NOA groups, and the 2 were highly correlated. It is likely that both BML and subchondral bone pathology (including sclerosis and cysts) contribute to the development of pain, but the temporal relationship of these pathologic features in the causal pathway of OA is unclear and cannot be elucidated given the cross-sectional design of our study.

Strengths of our study include its population-based design, which allows for generalizability of results to those with knee pain. The inclusion of the full spectrum of disease in this symptomatic population was unique and allowed for an evaluation of BML in PROA. Nearly half of our study cohort consisted of PROA. Although this stage of disease is presumed to be part of the continuum of OA, no data exist on how frequently PROA will progress to ROA. Nevertheless, we found an association of BML with pain severity in this cohort. To our knowledge, this is the first study to examine this type of population and to build upon the existing literature in earlier stages of OA.

BML were present in 11% of subjects with no OA, 38% with preradiographic OA, and 71% with radiographic OA. In our study of symptomatic early knee OA subjects, bone marrow lesions were significantly associated with pain on climbing stairs.

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