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The Within-Subregion Relationship between Bone Marrow Lesions and Subsequent Cartilage Loss in Knee Osteoarthritis

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Abstract

Bone marrow lesions are believed to increase risk of knee osteoarthritis (OA) progression. Whether their effect is local and whether it can be explained by other types of bone lesions concomitantly present in the same subregion is unclear. We evaluated bone lesion frequency in subregions without cartilage lesions and cartilage lesion frequency in subregions without bone lesions and investigated the within-subregion bone marrow lesion/subsequent cartilage loss relationship after adjusting for other types of bone lesions at baseline.

Individuals with knee OA had MRI at baseline and two years later. Bone marrow lesions, bone cysts, bone attrition, and cartilage integrity were scored within tibiofemoral subregions. Logistic regression with GEE to account for correlation among multiple subregions within a knee was used to estimate ORs for cartilage loss associated with bone marrow lesions adjusting for age, gender, BMI, and bone attrition and cysts in the same subregion.

Analyzing 1953 subregions among 177 knees, 90% of subregions had no bone lesion at baseline. Only 0–3% of subregions without cartilage lesions had bone lesions in the same subregion; in contrast, 5–33% of subregions without bone lesions had cartilage lesions. Bone marrow lesions at baseline were associated with 2 year cartilage loss in the same subregion, adjusting for other types of bone lesions at baseline (adjusted OR 3.74, 95% CI 1.59, 8.82).

In persons with knee OA, bone marrow lesions were rare at early disease stages but predicted subregional cartilage loss after accounting for the presence of other types of bone lesions in the same subregion.

INTRODUCTION

Bone underlying the cartilage surface of joints increases the contact area under load and reduces stresses within the cartilage (1). There has been a longstanding interest in the role of subchondral bone in the development and progression of osteoarthritis (OA) (2). Subchondral bone undergoes several changes in the setting of knee OA, including remodeling of the bone-cartilage interface, endochondral and intramembranous ossification

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of fibrovascular tissue penetrating the cartilaginous surface ultimately producing cartilage thinning and bone exposure, with other pathology including bone sclerosis, pseudocyst formation, and attrition. As much of what is known has come from animal model, tissue model, or cadaver studies, it remains unclear whether damage and loss of articular cartilage precede, accompany, or follow the development of lesions in subchondral bone, and what role bone lesions play in disease progression. MRI techniques cannot as yet routinely provide insight into the material properties and functional capacity of subchondral bone, but do afford an opportunity within longitudinal studies to examine the role of certain bone lesions *in vivo* in the natural history of human knee OA.

The subchondral bone marrow lesion, a non-cystic areas of ill-defined hyperintensity in T2-weighted, proton density-weighted, STIR or intermediate-weighted (IW) and hypointense in T1-weighted MRI images (3), has received attention as a potential risk factor for knee OA progression. In the BOKS (Boston Osteoarthritis Knee Study), bone marrow lesions at baseline were associated with subsequent radiographic (4) and MRI-based (5) measures of knee OA progression. A relationship between bone marrow lesions and worse cartilage integrity has been demonstrated in cross-sectional analyses (6) and in recent studies focusing on concurrent change (5,7,8). Certain questions regarding bone marrow lesions remain unanswered. Does their initial appearance precede or follow local cartilage lesion development? Is the effect on cartilage local? Is the effect explained by other bone lesions (i.e. subchondral bone attrition and cysts) in the vicinity?

Niu and Zhang introduced methodology to analyze the effect of a lesion on cartilage integrity locally, i.e. within the same articular surface subregion (9). While one study examining concurrent change in bone marrow lesions and cartilage applied a within-subregion approach (8), other reports describing the relationship between baseline bone marrow lesions (i.e. present at the beginning of the study period) and subsequent cartilage loss used a more traditional compartment level approach (4,5). Also, previous studies have not taken into account possible confounding from other types of bone pathology within the same subregion. A within-subregion approach provides an opportunity to explore the question of whether bone marrow lesions or cartilage lesions appear first, by examining the frequency of bone lesions in subregions free of cartilage lesions and of cartilage lesions in subregions free of bone lesions.

Our goals were, in knees from persons with knee OA, to determine:

1. in tibiofemoral surface subregions without any cartilage lesion, the frequency of subchondral bone lesions (i.e. bone marrow lesions, cysts, and attrition);
2. in subregions without any bone lesion, the frequency of cartilage lesions; and
3. whether the presence of bone marrow lesions at baseline is associated with worsening of cartilage integrity within the same tibiofemoral subregion over the next two years, after adjusting for bone attrition and bone cysts within the same subregion at baseline.

METHODS

Sample

Study participants were the members of a cohort of a natural history study of knee OA utilizing MRI, the MAK-2 Study (Mechanical Factors in Arthritis of the Knee-Study 2). MAK-2 cohort participants were recruited from community sources, letters to members of the registry of the Beuhler Center on Aging, Health and Society at the Feinberg School of Medicine at Northwestern University, and via medical center referrals.

Inclusion criteria were: definite tibiofemoral osteophyte presence [Kellgren/Lawrence (K/L) radiographic grade ≥ 2] in one or both knees; and Likert category of at least “a little difficulty” for two or more items in the WOMAC physical function scale. Exclusion criteria were: corticosteroid injection within the previous 3 months; history of avascular necrosis, rheumatoid or other inflammatory arthritis, periarticular fracture, Paget’s disease, villonodular synovitis, joint infection, ochronosis, neuropathic arthropathy, acromegaly, hemachromatosis, gout, pseudogout, osteopetrosis, or meniscectomy; or exclusion criteria for MRI such as presence of a pacemaker, artificial heart valve, aneurysm clip or shunt, metallic stent, implanted device (e.g. pain control/nerve stimulator, defibrillator, insulin/drug pump, ear implant), or any metallic fragment in an eye.

Approval was obtained from the Office for the Protection of Research Subjects- Institutional Review Boards of Northwestern University and Evanston Northwestern Healthcare. Written consent was obtained from all participants.

MRI Acquisition and Reading

All participants had MRI of both knees using a commercial knee coil and one of two whole-body scanners (1.5T in 162 participants or 3.0T in 15 participants, GE Healthcare, Waukesha, WI). Each participant was scanned and rescanned on the same machine and following the same protocol at the two time points (baseline and two-year follow-up). Sequences included axial and double oblique coronal T1-weighted 3D spoiled gradient-echo (SPGR) images with water excitation (T1 3D SPGR WE), coronal T1-weighted spin-echo (Cor T1 SE), and sagittal fat-suppressed dual-echo turbo SE (Sag FS dual-echo FSE).

The acquisition parameters for 1.5T were:

Sequence	TR (ms)/TE (ms)/FA (°)	FOV (cm)	Matrix size	Slice Thk / gap (mm)	Acquisition time (min)
Cor T1 SE	574/11/90	12	256×256	3.0/3.0	4:54
Sag dual echo FSE	3800/19,65/90	14	256×256	3.0/3.0	7:06
Axial & Cor T1 3D SPGR WE	17.2/7.85/10	16	512×512	1.5 / 0.0	8:51

The acquisition parameters for 3.0T were:

Sequence	TR (ms)/TE (ms)/FA (°)	FOV (cm)	Matrix size	Slice Thk / gap (mm)	Acquisition time (min)
Cor T1 SE	800/11/90	12	288×224	3.0/0.5	6:08
Sag dual echo FSE	3000/16,65/90	14	224×224	3.0/1.0	5:42
Axial & Cor T1 3D SPGR WE	18.2/5.7/15	16	512×512	1.5/0.0	9:00

Following a detailed reading protocol, each knee was scored using the whole-organ MRI scoring (WORMS) method (10). Specifically, three subregions (anterior, central, and posterior) of the medial and lateral femoral condyles and the medial and lateral tibial plateaus were each scored separately for subchondral bone marrow lesions, bone cysts, bone attrition, and cartilage integrity. For each lesion, each subregion received its own score.

At each subregion, cartilage morphology was scored on a seven point integer scale (0–6) defined as follows: 0 = normal thickness and signal; 1 = normal thickness but increased signal on T2-weighted images; 2 = solitary, focal, partial or full-thickness defect ≤ 1 mm in width; 3 = multiple areas of partial-thickness loss or a grade 2 lesion > 1 mm, with areas of preserved thickness; 4 = diffuse, > 75%, partial-thickness loss; 5 = multiple areas of full-thickness loss, or a full-thickness lesion > 1 mm, with areas of partial-thickness loss; and 6 = diffuse, > 75%, full-thickness loss. Cartilage lesion presence was defined as a score of 2 or greater.

Subchondral bone marrow lesions and bone cysts were each scored as integers from 0 to 3: 0 = normal; 1 = mild, < 25% of region; 2 = moderate, 25–50% of region; 3 = severe, > 50% of region. Subchondral bone attrition (flattening and depression of the articular surfaces) was scored from 0 to 3, for normal, mild, moderate, and severe, respectively. Bone marrow lesions, bone attrition, and bone cysts were considered present in a subregion if the corresponding score was > 0. MR images were read by one of three expert readers whose reliability with this scoring system has been published (10). The readers were blinded to the chronological order of the two acquisitions and to the hypotheses to be tested in this study.

Radiographic Acquisition and Reading

All participants had bilateral, anteroposterior, weightbearing knee radiographs at baseline in the semi-flexed position with fluoroscopic confirmation of superimposition of the anterior and posterior tibial plateau lines and centering of the tibial spines within the femoral notch (full protocol in 11). To describe the knees, the K/L global radiographic score was used (0 = normal; 1 = possible osteophytes; 2 = definite osteophytes without definite joint space narrowing; 3 = definite joint space narrowing, some sclerosis, and possible attrition; and 4 = large osteophytes, marked narrowing, severe sclerosis and definite attrition). Reliability for radiographic grading for the radiographic reader was high (Kappa coefficient 0.86).

Statistical Analysis

Data from the dominant knee (defined as the knee with which the participant would kick a ball) of each participant were analyzed. Twelve subregions were included per knee, 3 each from the medial tibial, medial femoral, lateral tibial, and lateral femoral surfaces. Subregions with the worst cartilage integrity score (= 6, or diffuse full-thickness loss of cartilage) were excluded as further worsening was not possible. The relationship between bone marrow lesions (presence vs. absence) at baseline and worsening of cartilage integrity (i.e. an increase in score by ≥ 1 point) between baseline and 2 years later within the same subregion was examined using logistic regression with generalized estimating equations (GEE) to account for correlation among multiple subregions within one knee. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived for each model. SAS software was used (Version 9.1; SAS Institute; Cary NC). Analyses were adjusted for age, gender, and body mass index (BMI) and further adjusted for other bone attrition and bone cysts within the same subregion at baseline.

RESULTS

Ten% of the 202 participants who completed the baseline evaluation did not participate in the two year follow-up evaluation, evenly distributed between these reasons: deceased, bilateral total knee replacement, moving away, or new MRI contraindication. Of the remaining 182 dominant knees (from 182 persons), 5 knees were excluded for missing subregional data. The sample consisted of 177 knees from 177 persons with a mean age of 66.2 years (± 11.5, S.D.) and a mean BMI of 30.3 kg/m^2 (± 6.2, S.D.). Of the 177 persons, 139 (79%) were women and 38 (21%) were men. The majority of knees (74%) were graded

K/L 2 or K/L 3. Of the 2124 subregions (177 knees, 12 subregions per knee), 171 subregions were excluded from all analyses for having advanced disease that could not progress further, i.e. a cartilage integrity score of 6 corresponding to diffuse, full-thickness loss of cartilage, leaving an analytic sample of 1953 subregions from 177 persons/knees.

In these 177 knees with 1953 subregions, 82 knees (46%) had a bone marrow lesion in at least one subregion at risk for progression, 68 (38%) had bone attrition in at least one subregion, and 39 knees (22%) had a bone cyst in at least one subregion. Of the 1953 regions, 1750 subregions (90%) had no bone marrow lesions, bone attrition, or bone cysts. Bone marrow lesions occurred alone in 71 subregions, bone attrition alone in 51 subregions, and bone cysts alone in 15 subregions. Twenty-five subregions had both bone marrow lesions and bone attrition, 17 subregions had bone marrow lesions and bone cysts, and 3 subregions had bone cysts and bone attrition, while 21 subregions had all 3 bone lesions.

Next, we determined the frequency of subchondral bone lesions in subregions without cartilage lesions and the frequency of cartilage lesions in subregions without bone lesions. As shown in Table 1, bone marrow lesions, bone attrition, and bone cysts were infrequently (less than or equal to 3% of the time) found in subregions without cartilage lesions. In subregions without any of these bone lesions, cartilage lesions were more frequent (5% to 33% of the time) (Table 2).

Table 3 shows the percentage of persons with each subchondral bone lesion in at least one subregion at risk for cartilage loss (i.e. with cartilage integrity score < 6). Among persons with a bone lesion in at least one subregion at risk for further cartilage loss, the average number of subregions with these bone lesions was relatively small, i.e. 1.4 to 1.6 subregions. The percentage of persons with cartilage loss in at least one subregion with a bone lesion ranged from 15% for bone cysts to 24% for bone attrition among persons at risk for cartilage loss (see Table 3).

We estimated the odds ratio for cartilage loss over a two year follow-up period (outcome variable) associated with the presence of bone marrow lesions within the same subregion. As shown in Table 4, cartilage loss was significantly associated with the presence of bone marrow lesions at baseline in the unadjusted model (OR 4.04, 95% CI 2.25, 7.26). This relationship persisted after adjustment for age, gender, and BMI (adjusted OR 3.88, 95% CI 2.12, 7.10) and after further adjustment for the presence other types of bone lesions within the same subregion (adjusted OR 3.74, 95% CI 1.59, 8.82). Bone attrition at baseline was significantly associated with cartilage loss in the same subregion after adjusting for age, gender, and BMI, but not after further adjustment for the other types of bone lesions (Table 4).

DISCUSSION

Our analyses show, in persons with knee OA, that the presence of bone marrow lesions at baseline was associated with a nearly 4-fold increase in the likelihood of worsening of cartilage integrity in the same subregion over the next two years after adjusting for other types of bone lesions within the same subregion. Baseline data revealed that many knees had a bone marrow lesion in at least one subregion, but 90% of subregions had no bone marrow lesion, no bone attrition, and no bone cysts. When a bone marrow lesion was present in a knee, on average it was present in a relatively small number, i.e. less than two subregions. Bone lesions were rare in subregions without cartilage lesions; cartilage lesions were more common in subregions without bone lesions.

Previous reports from the BOKS examining the relationship between the presence of bone marrow lesions at baseline and knee OA progression in a subsequent period revealed a

relationship at a compartment level, i.e. presence of any bone marrow lesion in a compartment was associated with any worsening of radiographic scores (4) or cartilage integrity in that compartment (5), adjusting for age, gender, and BMI. We were able to demonstrate this relationship within the same articular surface subregion, and, further, that the bone marrow lesion/cartilage worsening relationship was not explained by bone attrition or bone cysts that may have been present within the same subregion.

The analytic approach we applied for the analyses of multiple subregions within a knee is similar to that used by Roemer et al (8). The utility of using subregional MRI data to examine focal lesion effects was highlighted by Niu et al (9). They conducted a matched case-control study using knees that had all subregions eligible for cartilage loss at baseline and had cartilage loss in at least one site at follow-up. The subregions with cartilage loss (cases) were matched to the sites without cartilage loss (controls) within each knee. They used conditional logistic regression adjusting for the compartment.

A previous report of the subregional bone marrow lesion/cartilage worsening relationship from the MOST study focused upon whether bone marrow lesions and cartilage change together (8), an interesting but different question than we pose here. Roemer et al found that a persistent absence of bone marrow lesions over time was associated with a decreased risk of concurrent cartilage loss, while worsening and new bone marrow lesions were associated with a high risk of concurrent cartilage loss, adjusting for age, gender, BMI, and K/L grade (8). In the BOKS, Hunter et al found that an increase in bone marrow lesions was associated with a concurrent worsening of cartilage score at the compartment level (5). Raynauld et al found a relationship between concurrent cartilage volume loss and change in size of bone marrow lesions in the medial condyle and the medial tibial plateau (7). These studies consistently found that bone marrow lesions and cartilage get worse together.

Recent reports imply a need to consider other types of bone lesions in the analysis of the bone marrow lesion/cartilage loss relationship. In the MOST Study, bone marrow lesions were associated with prevalent and incident bone attrition in the same subregion, adjusting for age, gender, BMI, and ethnicity (12). Also, in other analyses from the MOST Study, bone attrition was associated with cartilage loss in the same subregion (13), and bone marrow lesions were associated with cysts in the same subregion (14). However, we were not able to find any reports of the bone marrow lesion/cartilage loss relationship in which analyses were adjusted for the presence of these other types of bone lesions.

We found no bone lesions in 90% of subregions. This is similar to results from the MOST Study in which 92% of subregions had no bone marrow lesions at baseline (8) and 95% of subregions had no bone cysts (14). A bone marrow lesion was present in at least one subregion in 62% of knees in the MOST Study (8) and in 57% of knees in the BOKS (5). The lower number (46%) in our study may reflect the fact that we excluded subregions with the most severe stage of disease (score of 6 or diffuse, full-thickness loss).

In an arthroscopic study, bone marrow lesions were present (per MRI reader blinded to arthroscopy findings) beneath 105 of 554 (19%) of articular cartilage defects but only 1% of articular surfaces that appeared normal at the time of surgery (6). Higher grades of articular cartilage defects were associated with a higher prevalence and greater depth and cross-sectional area of bone marrow lesions (6). In our examination of the baseline data, we found that bone marrow lesions, attrition, and cysts were each very rare in subregions free of any cartilage lesion. In contrast, cartilage lesions were more common in subregions free of any of these bone lesions.

Together, these arthroscopic results and our results support the possibility that cartilage lesions typically develop before bone marrow lesions and that bone marrow lesion

development depends upon the presence of preexisting cartilage damage. It is possible that bone marrow lesions have a deleterious effect on osteoarthritic disease that is already underway. However, it is important to acknowledge the alternative possibility, that bone marrow lesions are a local epiphenomenon of cartilage status with no impact on the rate of cartilage loss. This can be further explored in studies with more than two time points.

Our study has limitations. The WORMS method may be relatively insensitive in the detection of small changes. We used the cartilage integrity score from the WORMS as it enabled us to examine the relationship between bone marrow lesions and subsequent worsening of cartilage integrity within the same subregion. Despite the limitations of the WORMS method, we were able to detect this relationship. The relatively small number of men precluded analysis to confirm that the results were similar specifically for men.

It is important to emphasize that other aspects of subchondral bone structure and function may play a pivotal role in knee OA disease progression. The bone lesions that are the focus of our and other studies may not capture, except perhaps in an indirect way, key mechanical and material properties of subchondral bone, how it functions, how it handles load at the knee, and its ability to help articular cartilage. Methods to assess these subchondral bone parameters *in vivo* should be refined and applied in longitudinal studies.

In conclusion, in persons with knee OA, subchondral bone lesions were rare in tibiofemoral subregions without cartilage lesions; cartilage lesions were more common in subregions without bone lesions. The presence of bone marrow lesions at baseline was associated with worsening of cartilage integrity in the same tibiofemoral subregion over the next two years in analyses adjusting for bone attrition and cysts in the same subregion.

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REFERENCES

1. Burr, DB. Subchondral bone in the pathogenesis of osteoarthritis – Mechanical aspects. In: Brandt, K.; Doherty, M.; Lohmander, LS., editors. Osteoarthritis. Oxford: Oxford University Press; 2003. p. 125-133.
2. Garrod, AE. Rheumatoid arthritis, osteo-arthritis, arthritis deformans. In: Albutt, TC.; Rolleston, HD., editors. A System of Medicine. London: Macmillan; 1907. p. 3-43.
3. Roemer FW, Hunter DJ, Guermazi A. MRI-based semiquantitative assessment of subchondral bone marrow lesions in osteoarthritis research. Osteoarthritis Cartilage. 2008 Oct 21. [Epub ahead of print].
4. Felson DT, McLaughlin S, Goggins J, LaValley M, Gale ME, Totterman S, Li W, Hill C, Gale D. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med. 2003; 139:330–336. [PubMed: 12965941]
5. Hunter DJ, Zhang Y, Niu J, Goggins J, Amin S, LaValley MP, Guermazi A, Genant H, Gale D, Felson DT. Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. Arthritis Rheum. 2006; 54:1529–1535. [PubMed: 16646037]
6. Kijowski R, Stanton P, Fine J, De Smet A. Subchondral bone marrow edema in patients with degeneration of the articular cartilage of the knee joint. Radiology. 2006; 238:943–949. [PubMed: 16424243]
7. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Abram F, Choquette D, Haraoui B, Beary JF, Cline GA, Meyer JM, Pelletier JP. 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; 67:683–688. [Epub 2007 Aug 29]. [PubMed: 17728333]

8. Roemer FW, Guermazi A, Javaid MK, Lynch JA, Niu J, Zhang Y, Felson DT, Lewis CE, Torner J, Nevitt MC. 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. 2008 Oct 1. [Epub ahead of print].

9. Niu J, Hunter DJ, Felson DT, Guermazi A, Gale D, Zhang YQ. Evaluating the proximity of meniscal damage on risk of local cartilage loss using a matched case-control design. Arthritis Rheum. 2006; 54:S158.

10. Peterfy CG, Guermazi A, Zaim S, Tirman PFJ, Miaux Y, White D, Kothari M, Lu Y, Fye K, Zhao S, Genant H. Whole-organ magnetic resonance imaging score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage. 2004:177–190. [PubMed: 14972335]

11. Buckland-Wright CB. Protocols for precise radio-anatomical positioning of the tibiofemoral and patellofemoral compartments of the knee. Osteoarthritis Cart. 1995; 3 suppl A:71–80.

12. Roemer FW, Guermazi A, Neogi T, Zhu Y, Zhang Y, Javaid MK, Lynch JA, Crema MD, Marra MD, Torner J, Lewis CE, Felson DT, Nevitt MC. The association of MRI-detected tibiofemoral subchondral bone marrow lesions with prevalent and incident subchondral bone attrition: the MOST Study. Arthritis Rheum. 2008; 58:S697.

13. Neogi T, Zhang Y, Niu J, Lynch J, Nevitt M, Lewis CE, Wallace B, Felson D. Cartilage loss occurs in the same subregions as subchondral bone attrition: the MOST Study. Arthritis Rheum. 2008; 58:S235.

14. Crema MD, Roemer FW, Marra MD, Niu J, Zhu Y, Lynch J, Lewis CE, El-Khoury G, Felson DT, Guermazi A. MRI-detected bone marrow edema-like lesions are strongly associated with subchondral cysts in patients with or at risk for knee osteoarthritis: the MOST study. Osteoarthritis Cartilage. 2008; 16:S160.

Table 1

Frequency of Subchondral Bone Lesions in Subregions without Cartilage Lesions

Percentages represent the frequency of knees (among knees without a cartilage lesion in that subregion) with the specified bone lesion (i.e. bone marrow lesion, bone attrition, bone cyst) in that subregion, at baseline.

				In knees without any cartilage lesions in the subregion, number (%) with same subregion…		
Compartment	**Surface**	**Subregion**	**Number of knees without any cartilage lesion in the subregion**	**..bone marrow lesion**	**…bone attrition**	**…bone cyst**
Medial	femoral	anterior	110	1 (1%)	1 (1%)	0 (0%)
		central	98	1 (1%)	0 (0%)	0 (0%)
		posterior	134	3 (2%)	1 (1%)	1 (1%)
	tibial	anterior	153	3 (2%)	0 (0%)	5 (3%)
		central	107	0 (0%)	2 (2%)	0 (0%)
		posterior	146	1 (1%)	0 (0%)	3 (2%)
Lateral	femoral	anterior	110	3 (3%)	1 (1%)	2 (2%)
		central	126	0 (0%)	1 (1%)	0 (0%)
		posterior	146	1 (1%)	0 (0%)	1 (1%)
	tibial	anterior	157	2 (1%)	0 (0%)	3 (2%)
		central	132	1 (1%)	0 (0%)	0 (0%)
		posterior	153	2 (1%)	0 (0%)	2 (1%)

Table 2
Frequency of Cartilage Lesions in Subregions without Subchondral Bone Lesions

Percentages represent the frequency of knees (among knees without any bone lesions in that subregion) with a cartilage lesion in that subregion, at baseline.

Compartment	Surface	Subregion	Number of knees without any bone marrow lesion, bone attrition, or bone cyst in the subregion	In knees without any bone lesion, number (%) with a cartilage lesion in the same subregion
Medial	femoral	anterior	161	53 (33%)
		central	135	38 (28%)
		posterior	173	42 (24%)
	tibial	anterior	166	18 (11%)
		central	139	33 (24%)
		posterior	170	27 (16%)
Lateral	femoral	anterior	135	28 (21%)
		central	156	31 (20%)
		posterior	155	12 (8%)
	tibial	anterior	169	15 (9%)
		central	148	16 (11%)
		posterior	158	8 (5%)

Table 3

Person-Specific Extent of Subregion Involvement by Bone Lesion Type and Frequency of Cartilage Loss

The first column represents the percentage of the cohort of 177 persons/knees who had the specified bone lesion in at least one subregion that was at risk for worsening of cartilage integrity. The second and third columns represent, among persons with a specified bone lesion in at least one subregion at risk for worsening of cartilage integrity, the average number of subregions in that person's knee with the specified lesion, and the percentage of persons with worsening of cartilage integrity in at least one subregion with a bone lesion.

		For persons with given bone lesion in ≥ 1 subregion at risk for cartilage loss….	
Lesion	**Number (%) of 177 persons with specified bone lesion in ≥ 1 subregion at risk for cartilage loss**	**…average number of subregions/knee with specified lesion**	**…percentage of persons with cartilage loss in a subregion with a bone lesion**
Bone marrow lesion	82 (46%)	1.6	19/82 (23%)
Subchondral bone attrition	68 (38%)	1.5	16/68 (24%)
Subchondral bone cyst	39 (22%)	1.4	6/39 (15%)

Table 4

Odds Ratios (OR) for Worsening of Cartilage Integrity Between Baseline and Two Years Within the Same Subregion (n = 1953 subregions from 177 knees of 177 persons)

ORs and 95% confidence intervals (CI) are shown for each bone lesion: unadjusted; adjusted for age, gender, and BMI; and adjusted for age, gender, BMI, and other types of bone lesions within the same subregion.

Independent variable	Unadjusted OR (95% CI)	OR adjusted for age, gender, BMI (95% CI)	OR adjusted for age, gender, BMI and other types of bone lesions within the same region (95% CI)
Bone marrow lesion	4.04 (2.25, 7.26)	3.88 (2.12, 7.10)	3.74 (1.59, 8.82)
Subchondral bone cyst	1.68 (0.56, 5.00)	1.66 (0.55, 4.99)	0.47 (0.11, 2.03)
Subchondral bone attrition	3.17 (1.64, 6.16)	2.95 (1.46, 5.96)	1.85 (0.71, 4.82)