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Denuded Subchondral Bone and Knee Pain in Persons with Knee Osteoarthritis

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Abstract

How articular cartilage loss contributes to pain in persons with knee OA is unclear. Full thickness cartilage defects expose the subchondral bone plate. The relationship between denuded bone and pain has not been examined. We studied whether %denuded bone is associated: with moderate-severe knee pain or frequent knee pain; and longitudinally with incident frequent knee pain two years after the baseline evaluation.

We studied 182 persons with knee OA (305 knees). Applying specialized MRI techniques, manual segmentation was used to compute cartilage-covered and denuded bone areas for each surface. Moderate-severe knee pain was defined as ≥ 40 mm on knee-specific 100 mm VASs, and frequent knee pain as pain for most days in the past month. Logistic regression and GEE were used in analyses adjusting for age, gender, BMI, and bone marrow lesions.

Cross-sectional analyses revealed that moderate-severe knee pain was associated with %denuded bone in the medial compartment (adjusted OR 3.90, 95% CI 1.33, 11.47), medial and patellar surfaces together, and lateral and patellar surfaces. Frequent knee pain was associated with %denuded bone in the patellar surface (adjusted OR 3.11, 95% CI 1.24, 7.81), medial and patellar surfaces, and lateral and patellar surfaces. Longitudinal analyses (in 168 knees without baseline frequent knee pain) revealed that denuded bone in medial and patellar surfaces was associated with incident frequent knee pain (adjusted OR 4.19, 95% CI 1.56, 11.22).

These results support a relationship between subchondral bone plate exposure and prevalent and incident knee pain in persons with knee OA.

INTRODUCTION

Knee pain is the most common symptom experienced by persons with knee osteoarthritis (OA). Pathognomonic features of progressive knee OA, loss of articular cartilage and exposure of the subchondral bone plate, are believed to contribute to knee symptoms. How loss of articular cartilage contributes to pain remains unclear. Structural changes of OA reported in the literature correlate only modestly with knee pain. Insight into the structural change/pain relationship will improve understanding of the origins and pathophysiology of pain in knee OA. Subchondral bone has attracted attention as a possible source of pain, in part because of its intimate relationship with the overlying cartilage, its rich innervation, and its response to dynamic loading. In support of this, at least three previous cross-sectional reports (1-3) and one longitudinal study (4) have suggested that bone marrow lesions are associated with knee pain, although other studies have not found evidence of this relationship (5-7).

Knee articular cartilage covers the subchondral bone plate and helps to attenuate knee loads sustained during activity. Loss of this load-attenuating tissue leaves bone nociceptors more exposed and vulnerable to mechanical insult. Specialized MR image acquisition and measurement techniques have been developed to quantify the area of exposed bone in osteoarthritic knees (8,9), termed the denuded area of bone (dAB) (10). The extent of denuded subchondral bone can be expressed as the percentage that is uncovered (%dAB) of the total of both cartilage-covered and uncovered subchondral bone area of a specific joint surface (10). It is important to determine whether the %denuded bone, a putative surrogate imaging biomarker, is directly related to clinical endpoints such as pain. It is not known whether the presence or extent of denuded bone at any of the knee joint surfaces is associated with the severity of knee pain, frequency of knee pain, or a greater risk of developing frequent knee pain over time. It is also not known in which of the joint compartments denuded bone has the greatest impact on these aspects of pain.

Our study focused on the cross-sectional and longitudinal relationship between %denuded bone and knee pain in persons with knee OA. We examined the relationships between denuded bone – separately for the medial compartment, the lateral compartment, the patellar surface, and each tibiofemoral compartment in conjunction with the patellar surface – and knee pain. We specifically assessed whether:

- a. greater %denuded bone is associated with the presence of *moderate to severe knee pain* at the initial evaluation (baseline);
- b. greater %denuded bone is associated with the presence of *frequent knee pain* at baseline; and
- c. in knees without frequent knee pain at baseline, greater %denuded bone at baseline is associated with an increased risk for development of frequent knee pain at two years.

METHODS

Sample

Study participants are the members of a cohort of a natural history study of knee OA, the MAK-2 Study (Mechanical Factors in Arthritis of the Knee-Study 2). MAK-2 participants were recruited from community sources, e.g. through advertising in periodicals targeting elderly persons, neighborhood organizations, letters to members of the registry of the Buehler Center on Aging, Health and Society at Northwestern University, and via medical center referrals.

Inclusion criteria for our study 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 three 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

All participants had MRI of both knees using a commercial knee coil and one of two whole-body scanners, 1.5T or 3.0T (GE Healthcare, Waukesha, WI); it has been shown that there are no systematic off-sets and that there exists a very high measurement correlation between these magnetic field strengths (11). Quantitative measurements of tibiofemoral and patellar denuded bone were obtained from axial and double oblique coronal T1-weighted 3D spoiled gradient-echo (SPGR) images with water excitation (T1 3D SPGR WE) sequences, after segmentation of the subchondral bone area and area of the cartilage surface. Grading of bone marrow lesions was performed based on coronal T1-weighted spin-echo (Cor T1 SE) and sagittal fat-suppressed dual-echo turbo SE (Sag FS dual-echo FSE) sequences.

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

Quantification of Denuded Subchondral Bone on MR Images

The total area of subchondral bone [tAB according to the standard nomenclature (10)] and the area of the cartilage surface were segmented by manually tracing the bone interface and cartilage surface in each section for the medial tibial, lateral tibial, weightbearing portion of the medial and lateral femoral condyle, and the patellar surfaces. Segmentation was performed by ten readers with systematic standardized training and experience in knee cartilage segmentation, using custom software (Chondrometrics GmbH, Ainring, Germany) (11-13). All segmentations (each slice in each cartilage plate) were checked for quality by one expert (F.E.). The readers and the quality control reader were blinded to the hypotheses

to be tested in this study and to all other data. Among other parameters (cartilage volume and thickness), the total subchondral bone area (tAB), area of subchondral bone covered with cartilage (cAB), and the denuded area of bone (dAB) were computed using the software noted above, as previously described (14). Evidence of excellent reliability (as the coefficient of variation, for two acquisitions with repositioning) using the acquisition protocol applied here, image analysis by experienced readers from the same group as in the current study, and Chondrometrics software, has been published for both 1.5T and 3.0T (11).

MR Image Reading for Bone Marrow Lesion Score

Three regions (anterior, central, and posterior) of the medial and lateral femoral condyles and tibial plateaus and two regions of the patellar surface (medial and lateral) were each scored separately for subchondral bone marrow lesions using the whole-organ MRI scoring (WORMS) system (15). Subchondral bone marrow lesions were 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. The score used in analysis was the worst score among the regions of the surfaces under consideration. MR images were read by one of three experienced readers (different from those who performed the cartilage segmentation and quality control). Inter-rater reliability for these readers applying this scoring system has been published [e.g. inter-reader agreement (intraclass correlation coefficient, ICC) for these readers for bone marrow lesions was 0.90, 0.96, and 0.82 for medial, lateral, and patellofemoral regions, respectively (15)]. Readers were blinded to the hypotheses to be tested in this study and to all other data.

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 16). 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 single x-ray reader was high (Kappa coefficient 0.86).

Measurement of Knee Pain

Knee pain severity over the past week was measured using 100 mm visual analogue scales (VASs), with separate scales for the right and left knees. The scales were anchored at 0 for “no pain” and at 100 for “pain as bad as it could be”, with standardized instructions. Frequent knee pain was assessed by asking the question (separately for the right and left knees), “Did you have pain in or around your knee for most days in the past month?”

Statistical analysis

All knee pain measures used were specific to each knee, and all analyses were at the level of the knee (not at the level of the person). We used generalized estimating equations (GEE), which addresses the potential correlation between measurements (i.e. the right and left knee) within one person. Knees with total knee replacement at either baseline or the two year visit were excluded. All persons had knee OA (K/L ≥ 2) in at least one knee; both knees were included in analyses. Percent denuded subchondral bone was calculated as:

$$\% \text{denuded bone} = \left[\frac{\text{(sum of the denuded area of bone for surfaces of interest)}}{\text{(total area of bone for same surfaces)}} \right] \times 100$$

To examine the first (cross-sectional) question, we used logistic regression analysis with GEE to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between presence of moderate to severe knee pain and %denuded bone at combinations of joint surfaces using the baseline data. We report analyses of %denuded bone in the medial tibiofemoral compartment (medial tibia + medial weightbearing femur), the lateral tibiofemoral compartment (lateral tibia + lateral weightbearing femur), the patellar surface, the medial tibiofemoral compartment and patellar surface together, and the lateral tibiofemoral compartment and patellar surface together. For these models, %denuded bone was stratified into 3 categories, and modeled using two indicator variables: no denuded bone (%denuded bone = 0, reference group); non-zero and less than or equal to the median (i.e. the median of non-zero values for the given cartilage surfaces); and non-zero and greater than the median. Denuded bone was categorized due to its bimodal distribution; a subset of observations was clustered at 0 and there was a separate distribution of non-zero observations. Three categories addressed the possibility that the influence of a smaller area of denuded bone was similar to having no denuded bone. The median values of the non-zero %denuded bone measurements were 9.53%, 5.85%, 13.00%, 6.51%, and 5.65%, for the medial surfaces, lateral surfaces, patellar surface, medial + patellar surfaces, and lateral + patellar surfaces, respectively. The dependent variable, presence of moderate to severe knee pain (yes vs. no) in a specific knee, was defined as having a knee pain severity score ≥ 40 mm (on the 0-100 mm VAS) (17-19).

The same approach was taken to examine the second cross-sectional question, in which the dependent variable was the presence of frequent knee pain (yes vs. no) in a specific knee, as determined by the participant's answer to the question "Did you have pain in or around the knee for most days in the past month?"

Finally, using similar statistical methods for analyses, we estimated the ORs and 95% CIs for the association between incident frequent knee pain two years after the baseline evaluation and %denuded bone at the given surfaces at baseline. Only knees without frequent knee pain at baseline were included in this analysis. The median values of the non-zero %denuded bone measurements were 5.87%, 6.53%, 10.00%, 4.33%, and 4.96%, for the medial surfaces, lateral surfaces, patellar surface, medial + patellar surfaces, and lateral + patellar surfaces, respectively. The dependent variable for this analysis was the response to the question asking about frequent knee pain at the 2-year follow-up (yes vs. no) in a specific knee.

In reporting the result from each analysis, the ORs and 95% CIs: from the first logistic model presented are unadjusted [i.e. only %denuded bone (categorized) was entered as an independent variable]; from the second model, adjusted for age, gender, and body mass index (BMI); and from the third model, adjusted for age, gender, BMI, and bone marrow lesion score. The bone marrow lesion score used in analyses was the worst score among all regions in the surfaces under consideration. All analyses were done using SAS Version 9.1 (SAS Institute, Cary, NC).

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. 305 knees from 182 participants with knee OA in one or both knees were analyzed. These participants had a mean age of 66.1 years (± 11.3 , standard deviation), mean BMI of 30.1 kg/m² (± 5.9), and 142 of 182 (78%) were women. The K/L grade of these knees was 0 in 5 (2%) knees, K/L 1 in 25 knees (8%), K/L 2 in 123 knees (40%), K/L 3 in 106 knees (35%), and K/L 4 in 46

knees (15%). Among the 305 knees, the number of knees with no denuded bone was: 237 (78% of 305 knees) for the medial tibia + medial weightbearing femur; 224 (73%) for the lateral tibia + lateral weightbearing femur; 210 (69%) for the patella; 160 (52%) for the medial tibia + medial weightbearing femur + patella; and 155 (51%) for the lateral tibia + lateral weightbearing femur + patella.

Of the 305 knees, 97 (32%) had moderate to severe knee pain at baseline and 208 (68%) did not. As shown in Table 1, moderate to severe knee pain presence was cross-sectionally associated with having any denuded bone in the medial compartment surfaces (i.e. each of the categories of %denuded bone that exceeded 0) adjusting for age, gender, BMI, and bone marrow lesion score [adjusted ORs for each of the two categories of %denuded bone 4.31 (95% CI 1.46, 12.77) and 3.90 (95% CI 1.33, 11.47)]. A significant association between %denuded bone and moderate to severe knee pain presence was also found when the denuded bone was considered at the medial and patellar surfaces together, but not for the lateral surfaces. When %denuded bone was considered at the lateral and patellar surfaces together, %denuded bone greater than the median was associated with moderate to severe knee pain. Bone marrow lesion score was not significantly associated with moderate to severe knee pain presence in these models.

We next considered the cross-sectional relationship between %denuded bone and the presence of frequent knee pain at baseline. Of 305 knees, 137 (45%) had frequent knee pain at baseline and 168 (55%) did not. As shown in Table 2, the presence of frequent knee pain was associated with %denuded bone, in the higher category of %denuded bone at the patellar surface, adjusting for age, gender, BMI, and bone marrow lesion score [adjusted OR 3.11 (95% CI 1.24, 7.81)], at the medial compartment and patellar surface together [adjusted OR 3.17 (95% CI 1.53, 6.57)] and at the lateral compartment and patellar surface together [adjusted OR 2.94 (95% CI 1.42, 6.05)]. Bone marrow lesion score was not related to frequent knee pain presence in these models.

The longitudinal analyses included only those 168 knees (from 117 participants) without frequent knee pain at baseline. In these participants, the mean age was 68.5 years (± 11.4), mean BMI was 28.8 kg/m² (± 5.2), and 74% were women. In these knees, the K/L grade was 0 in 5 of 168 knees (3%), K/L 1 in 18 knees (11%), K/L 2 in 75 knees (45%), K/L 3 in 56 knees (33%), and K/L 4 in 14 knees (8%). Of the 168 knees, at baseline, the number with no denuded bone was 141 (84% of 168 knees) for the medial compartment, 131 (78%) for the lateral compartment, 100 (60%) for the medial and patellar surfaces, and 96 (57%) for the lateral and patellar surfaces.

At follow-up two years later, 48 knees (29% of the 168 knees) had developed frequent knee pain. As shown in Table 3, baseline-to-two year incident frequent knee pain was significantly associated with the higher category of %denuded bone at baseline in the medial and patellar surfaces together, adjusting for age, gender, BMI, and bone marrow lesion score [adjusted OR 4.19 (95% CI 1.56, 11.22)]. Bone marrow lesion score in the lateral compartment was significantly associated with incident frequent knee pain.

DISCUSSION

Our results show that, after controlling for age, gender, BMI, and bone marrow lesion score, moderate to severe knee pain presence at baseline was associated with the presence of denuded bone in the medial compartment, in the medial and patellar surfaces considered together, and (when %denuded bone exceeded the median of the non-zero values) in the lateral and patellar surfaces considered together, but not in the lateral compartment considered separately. Having frequent knee pain at baseline was associated with %denuded

bone (greater than the median) in the patellar surface alone, in the medial and patellar surfaces considered together, and in the lateral and patellar surfaces, but not in the medial or lateral surfaces when each was considered separately. In the longitudinal analysis of knees without frequent knee pain at baseline, denuded bone (greater than the median) in the medial and patellar surfaces considered together was associated with a greater likelihood of the new development of frequent knee pain at two years, when compared to knees without any denuded bone.

There are limitations to this study. The frequent pain question is an established and widely used measure that affords a model to look at both cross-sectional and longitudinal questions. There is no established approach for the longitudinal analysis of pain severity. In this study, denuded bone was examined as a percentage of a given surface. It was not feasible for us to consider either the number of regions of denuded bone or the size of individual denuded regions within a surface. Future studies should examine whether: there is a threshold denuded bone lesion size that corresponds with the perception of knee pain; this threshold varies by compartment; multiple small lesions produce the same pain as one large lesion.

To our knowledge, this is the first report (either cross-sectional or longitudinal) of the denuded bone/knee pain relationship. Prior studies examining the relationship between subchondral bone using MRI and knee pain have emphasized bone marrow lesions. In MOST (the Multicenter Osteoarthritis Study), frequent knee symptom development was associated with a concurrent increase in bone marrow lesion score (4). Among cross-sectional reports, in BOKS (Boston Osteoarthritis Knee Study), bone marrow lesions were more common in OA knees with than without symptoms (1), and in the SEM (Southeast Michigan) OA cohort, larger bone marrow lesions were more frequent in OA knees with than without pain (2). Torres et al in a previous report from our study found a cross-sectional relationship between bone marrow lesion score and knee pain severity in persons with knee OA (3). In two other studies, however, a bone marrow lesion/pain relationship was not detected (5-7).

It was necessary in the current study to adjust for bone marrow lesion score as a potential confounder. In models adjusting for age, gender, BMI, and %denuded bone, bone marrow lesion score was not significantly associated with prevalent pain, and only in the lateral compartment predicted incident frequent knee pain. Subchondral bone plate exposure may lie within the causal pathway between *other* tissue lesions and knee pain. Adjusting for these lesions oversimplifies the situation; there are many possible interpretations of preservation or attenuation of the %denuded bone/pain relationship in such a model. To explore the sequence of actions of these factors employing statistical modeling is of interest, but, because it hinges upon more than two evaluation time points, this is beyond the scope of the current study.

Our results suggest that denuded bone in the medial tibiofemoral compartment had the strongest (of the knee compartments) relationship to current moderate to severe pain. Knees with denuded bone in the medial compartment regardless of its extent (i.e. whether greater than or less than the median) were 4 times more likely to have moderate-severe knee pain than knees with no denuded bone. It did not appear to strengthen the relationship with moderate to severe pain to consider the medial and patellar surfaces together (vs. considering the medial compartment alone). On the other hand, the relationship between denuded bone and current frequent knee pain was found only when the denuded bone was considered at the patellar surface or at either of the tibiofemoral compartments in conjunction with the patellar surface. In the longitudinal analyses, denuded bone in the medial and patellar surface considered together (when greater than the median) was associated with an elevated risk for developing frequent knee pain.

A stronger relationship for the medial tibiofemoral compartment or the combined medial tibiofemoral and patellar surfaces is biologically and mechanically plausible. Even in healthy knees, more load is transmitted across the medial than the lateral compartment. Joint changes accompanying medial OA (which is substantially more common than lateral OA) further increase the proportion of load distributed medially. In view of this, exposed bone in the medial compartment may have the greatest impact on knee pain severity.

Tibiofemoral OA typically involves either the medial or lateral compartment in isolation or either compartment in conjunction with the patellofemoral compartment. A relationship with frequent pain was detected only with %denuded bone at the patellar surface or when both tibiofemoral and patellar surfaces were considered together. Theoretically, the risk factor profile for pain severity and pain frequency may not be identical, as these results illustrate, and ideally both should be examined. That it was at the patellar surface at which %denuded bone seemed to be most strongly related to frequent knee pain is in keeping with the central role played by the patellofemoral joint in daily activities.

In conclusion, moderate to severe knee pain presence at baseline was associated with the presence of denuded bone in the medial tibiofemoral compartment, in the medial and patellar surfaces considered together, and (when %denuded bone exceeded the median) in the lateral and patellar surfaces considered together, independent of bone marrow lesion score. Having frequent knee pain at baseline was associated with denuded bone (exceeding the median) in the patellar surface, in the medial and patellar surfaces considered together, and in the lateral and patellar surfaces. Denuded bone (exceeding the median) in the medial and patellar surfaces was associated with a greater likelihood of the new development of frequent knee pain at two years. These results support a relationship between subchondral bone plate exposure and prevalent and incident knee pain in persons with knee OA.

REFERENCES

- 1). Felson DT, Chaisson CE, Hill CL, Totterman SMS, Gale ME, Skinner KM, et al. The association of bone marrow lesions with pain in knee osteoarthritis. *Ann Intern Med.* 2001; 134:541–9. [PubMed: 11281736]
- 2). Sowers MF, Hayes C, Jamadar D, Capul D, Lachance L, Jannausch M, et al. Magnetic resonance-detected subchondral bone marrow and cartilage defect characteristics associated with pain and x-ray defined knee osteoarthritis. *Osteoarthritis Cartilage.* 2003; 11:387–93. [PubMed: 12801478]
- 3). 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. Epub 2006 May 18. [PubMed: 16713310]
- 4). Felson DT, Niu J, Guermazi A, Roemer F, Aliabadi P, Clancy M, et al. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. *Arthritis Rheum.* 2007; 56:2986–92. [PubMed: 17763427]
- 5). Link TM, Steinbach LS, Ghosh S, Ries M, Lu Y, Lane N, et al. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology.* 2003; 226:373–81. [PubMed: 12563128]
- 6). Kornaat PR, Bloem JL, Ceulemans RY, Riyazi N, Rosendaal FR, Nelissen RG, et al. Osteoarthritis of the knee: association between clinical features and MR imaging findings. *Radiology.* 2006; 239:811–7. [PubMed: 16714463]
- 7). Kornaat PR, Kloppenburg M, Sharma R, Botha-Scheepers SA, Le Graverand MP, Coene LN, et al. Bone marrow edema-like lesions change in volume in the majority of patients with osteoarthritis; associations with clinical features. *Eur Radiol.* 2007; 17:3073–8. Epub 2007 Sep 7. [PubMed: 17823802]

- 8). Eckstein F, Cicuttini F, Raynauld JP, Waterton JC, Peterfy C. Magnetic resonance imaging (MRI) of articular cartilage in knee osteoarthritis (OA): morphological assessment. *Osteoarthritis Cartilage*. 2006; 14(Suppl 1):46–75. Epub 2006 May 19.
- 9). Eckstein F, Burstein D, Link TM. Quantitative MRI of cartilage and bone: degenerative changes in osteoarthritis. *NMR Biomed*. 2006; 19:822–54. [PubMed: 17075958]
- 10). Eckstein F, Ateshian G, Burgkart R, Burstein D, Cicuttini F, Dardzinski B, et al. Proposal for a nomenclature for magnetic resonance imaging based measures of articular cartilage in osteoarthritis. *Osteoarthritis Cartilage*. 2006; 14:974–83. [PubMed: 16730462]
- 11). Eckstein F, Charles HC, Buck RJ, Kraus VB, Remmers AE, Hudelmaier M, et al. Accuracy and precision of quantitative assessment of cartilage morphology by magnetic resonance imaging at 3.0T. *Arthritis Rheum*. 2005; 52:3132–6. [PubMed: 16200592]
- 12). 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. [PubMed: 18512777]
- 13). Eckstein F, Wirth W, Hudelmaier M, Stein V, Lengfelder V, Cahue S, et al. Patterns of femorotibial cartilage loss in knees with neutral, varus, and valgus alignment. *Arthritis Rheum*. 2008; 59:1563–70. [PubMed: 18975356]
- 14). Hohe J, Ateshian G, Reiser M, Englmeier KH, Eckstein F. Surface size, curvature analysis, and assessment of knee joint incongruity with MRI in vivo. *Magn Reson Med*. 2002; 47:554–61. [PubMed: 11870843]
- 15). Peterfy CG, Guermazi A, Zaim S, Tirman PFJ, Miaux Y, White D, et al. Whole-organ magnetic resonance imaging score (WORMS) of the knee in osteoarthritis. *Osteoarthritis Cartilage*. 2004; 12:177–90. [PubMed: 14972335]
- 16). 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.
- 17). Collins SL, Moore A, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimeters? *Pain*. 1997; 72:95–7. [PubMed: 9272792]
- 18). Hartrick CT, Kovan JP, Shapiro S. The numeric rating scale for clinical pain measurement: a ratio measure? *Pain Practice*. 2003; 3:310–6. [PubMed: 17166126]
- 19). Krebs EE, Carey TS, Weinberger M. Accuracy of the pain numeric rating scale as a screening test in primary care. *J Gen Intern Med*. 2007; 22:1453–8. [PubMed: 17668269]

Cross-sectional relationship between presence of moderate to severe knee pain and %denuded bone at baseline (n = 305 knees from 182 persons)

Table 1

Surface(s) at which %denuded bone was measured	Independent variables		Unadjusted OR (95% CI) Logistic Model 1 *	Adjusted OR (95% CI) Logistic Model 2 **	Adjusted OR (95% CI) Logistic Model 3 ***
Medial tibia + medial weightbearing femur	%denuded bone	≤ median (vs. 0%)	3.18 (1.41, 7.16)	4.18 (1.51, 11.54)	4.31 (1.46, 12.77)
		> median (vs. 0%)	2.82 (1.28, 6.23)	3.60 (1.63, 7.95)	3.90 (1.33, 11.47)
Lateral tibia + lateral weightbearing femur	Bone marrow lesion score		-	-	0.95 (0.63, 1.44)
	%denuded bone	≤ median (vs. 0%)	1.63 (0.76, 3.48)	1.45 (0.67, 3.14)	1.46 (0.68, 3.16)
		> median (vs. 0%)	1.57 (0.72, 3.40)	1.89 (0.79, 4.51)	1.97 (0.82, 4.74)
Patella	Bone marrow lesion score		-	-	0.96 (0.70, 1.31)
	%denuded bone	≤ median (vs. 0%)	1.77 (0.90, 3.48)	1.71 (0.78, 3.75)	1.76 (0.79, 3.92)
		> median (vs. 0%)	1.39 (0.64, 3.00)	1.42 (0.60, 3.32)	1.55 (0.58, 4.12)
Medial tibia + medial weightbearing femur + patella	Bone marrow lesion score		-	-	0.92 (0.57, 1.50)
	%denuded bone	≤ median (vs. 0%)	2.64 (1.40, 4.96)	2.51 (1.23, 5.13)	2.41 (1.17, 4.99)
		> median (vs. 0%)	2.70 (1.38, 5.27)	3.12 (1.55, 6.29)	2.80 (1.30, 6.02)
Lateral tibia + lateral weightbearing femur + patella	Bone marrow lesion score		-	-	1.12 (0.81, 1.55)
	%denuded bone	≤ median (vs. 0%)	1.62 (0.84, 3.11)	1.58 (0.79, 3.15)	1.64 (0.82, 3.27)
		> median (vs. 0%)	1.92 (0.99, 3.70)	2.25 (1.09, 4.65)	2.57 (1.22, 5.42)
	Bone marrow lesion score		-	-	0.87 (0.63, 1.21)

The table shows the odds ratios (ORs) and 95% confidence intervals (CIs) from the logistic regression models for the association between presence of moderate to severe knee pain (dependent variable) and %denuded bone at the given surfaces using the baseline data. Statistically significant associations (95% CI excludes 1.00) are shown bolded.

* Logistic Model 1 covariates: %denuded bone

** Logistic Model 2 covariates: %denuded bone, age, gender, BMI

*** Logistic Model 3 covariates: %denuded bone, age, gender, BMI, bone marrow lesion score

Table 2

Cross-sectional relationship between prevalent frequent knee pain and %denuded bone at baseline (n = 305 knees from 182 persons)

Surface(s) at which %denuded bone was measured	Independent variables		Unadjusted OR (95% CI) Logistic Model 1 *	Adjusted OR (95% CI) Logistic Model 2 **	Adjusted OR (95% CI) Logistic Model 3 ***
Medial tibia + medial weightbearing femur	%denuded bone	≤ median (vs. 0%)	2.10 (0.98, 4.51)	2.36 (0.90, 6.19)	1.98 (0.72, 5.41)
		> median (vs. 0%)	2.37 (1.02, 5.50)	2.91 (1.30, 6.54)	1.69 (0.64, 4.45)
	Bone marrow lesion score		-	-	1.37 (0.96, 1.97)
Lateral tibia + lateral weightbearing femur	%denuded bone	≤ median (vs. 0%)	1.91 (0.97, 3.73)	1.70 (0.85, 3.40)	1.62 (0.82, 3.21)
		> median (vs. 0%)	1.48 (0.71, 3.06)	1.85 (0.82, 4.18)	1.40 (0.59, 3.34)
	Bone marrow lesion score		-	-	1.34 (0.98, 1.85)
Patella	%denuded bone	≤ median (vs. 0%)	0.81 (0.43, 1.53)	0.74 (0.36, 1.54)	0.78 (0.37, 1.64)
		> median (vs. 0%)	2.40 (1.15, 5.02)	2.70 (1.20, 6.07)	3.11 (1.24, 7.81)
	Bone marrow lesion score		-	-	0.88 (0.57, 1.35)
Medial tibia + medial weightbearing femur + patella	%denuded bone	≤ median (vs. 0%)	1.16 (0.67, 2.02)	1.03 (0.55, 1.92)	0.94 (0.50, 1.78)
		> median (vs. 0%)	3.13 (1.66, 5.91)	3.97 (2.02, 7.83)	3.17 (1.53, 6.57)
	Bone marrow lesion score		-	-	1.26 (0.91, 1.73)
Lateral tibia + lateral weightbearing femur + patella	%denuded bone	≤ median (vs. 0%)	1.28 (0.73, 2.25)	1.22 (0.67, 2.24)	1.17 (0.63, 2.18)
		> median (vs. 0%)	2.44 (1.34, 4.44)	3.36 (1.71, 6.63)	2.94 (1.42, 6.05)
	Bone marrow lesion score		-	-	1.15 (0.83, 1.59)

The table shows the odds ratios (ORs) and 95% confidence intervals (CIs) from the logistic regression models for the association between presence of frequent knee pain (dependent variable) and %denuded bone at the given surfaces using the baseline data. Statistically significant associations (95% CI excludes 1.00) are shown bolded.

* Logistic Model 1 covariates: %denuded bone

** Logistic Model 2 covariates: %denuded bone, age, gender, BMI

*** Logistic Model 3 covariates: %denuded bone, age, gender, BMI, bone marrow lesion score

Longitudinal relationship between incident frequent knee pain two years after baseline and %denuded bone at baseline (n = 168 knees from 117 persons)

Table 3

Surface(s) at which %denuded bone was measured	Independent variables		Unadjusted OR (95% CI) Logistic Model 1 *	Adjusted OR (95% CI) Logistic Model 2 **	Adjusted OR (95% CI) Logistic Model 3 ***
Medial tibia + medial weightbearing femur	%denuded bone	≤ median (vs. 0%)	0.78 (0.20, 3.07)	0.59 (0.14, 2.47)	0.47 (0.11, 2.07)
		> median (vs. 0%)	1.96 (0.59, 6.53)	2.79 (0.70, 11.15)	1.57 (0.35, 7.06)
	Bone marrow lesion score		-	-	1.41 (0.86, 2.33)
Lateral tibia + lateral weightbearing femur	%denuded bone	≤ median (vs. 0%)	1.78 (0.66, 4.78)	1.52 (0.52, 4.45)	1.44 (0.51, 4.05)
		> median (vs. 0%)	0.31 (0.07, 1.40)	0.27 (0.05, 1.48)	0.16 (0.02, 1.12)
	Bone marrow lesion score		-	-	1.70 (1.07, 2.69)
Patella	%denuded bone	≤ median (vs. 0%)	0.99 (0.35, 2.84)	0.96 (0.30, 3.01)	0.73 (0.22, 2.52)
		> median (vs. 0%)	4.08 (1.46, 11.43)	3.48 (1.20, 10.07)	2.10 (0.62, 7.23)
	Bone marrow lesion score				1.67 (0.92, 3.04)
Medial tibia + medial weightbearing femur + patella	%denuded bone	≤ median (vs. 0%)	0.92 (0.33, 2.55)	0.70 (0.21, 2.29)	0.68 (0.20, 2.30)
		> median (vs. 0%)	4.49 (1.76, 11.45)	4.68 (1.78, 12.27)	4.19 (1.56, 11.22)
	Bone marrow lesion score		-	-	1.14 (0.72, 1.81)
Lateral tibia + lateral weightbearing femur + patella	%denuded bone	≤ median (vs. 0%)	1.32 (0.57, 3.07)	1.30 (0.53, 3.19)	1.17 (0.46, 2.95)
		> median (vs. 0%)	1.70 (0.69, 4.17)	1.57 (0.61, 4.09)	1.10 (0.38, 3.21)
	Bone marrow lesion score		-	-	1.37 (0.90, 2.10)

The table shows the odds ratios (ORs) and 95% confidence intervals (CIs) from the logistic regression models for the association between incident frequent knee pain two years after baseline (dependent variable) and %denuded bone at the given surfaces at baseline. Only knees without frequent knee pain at baseline were included. Statistically significant associations (95% CI excludes 1.00) are shown bolded.

* Logistic Model 1 covariates: %denuded bone

** Logistic Model 2 covariates: %denuded bone, age, gender, BMI

*** Logistic Model 3 covariates: %denuded bone, age, gender, BMI, bone marrow lesion score