Title

Prevalent cartilage damage and cartilage loss over time are associated with incident bone marrow lesions in the tibiofemoral compartments: the MOST study

Journal

Osteoarthritis and Cartilage, 21(2)

ISSN

1063-4584

Authors

Crema, MD
Felson, DT
Roemer, FW
et al.

Publication Date

2013-02-01

DOI

10.1016/j.joca.2012.11.005

Peer reviewed

Published in final edited form as:
Osteoarthritis Cartilage. 2013 February ; 21(2): 306–313. doi:10.1016/j.joca.2012.11.005.

Prevalent cartilage damage and cartilage loss over time are associated with incident bone marrow lesions in the tibiofemoral compartments: the MOST Study

Michel D. Crema, MD[1,2], **David T. Felson, MD, MPH**[3], **Frank W. Roemer, MD**[1,4], **Ke Wang, DSc**[3], **Monica D. Marra, MD**[1], **Michael C. Nevitt, PhD, MPH**[5], **John A. Lynch, PhD**[5], **James Torner, PhD, MS**[6], **Cora E. Lewis, MD, MSPH, FACP, FAHA**[7], and **Ali Guermazi, MD**[1]

[1]Department of Radiology, Quantitative Imaging Center, Boston University School of Medicine, Boston, MA

[2]Department of Radiology, Hospital do Coração (HCor), and Teleimagem, São Paulo, Brazil

[3]Clinical Epidemiology Research & Training Unit, Boston University School of Medicine, Boston, MA

[4]Department of Radiology, Klinikum Augsburg, Augsburg, Germany

[5]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA

[6]Department of Epidemiology, University of Iowa, Iowa City, IA

[7]Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham

Abstract

Objective—To assess the association of prevalent cartilage damage and cartilage loss over time with incident bone marrow lesions (BMLs) in the same subregion of the tibiofemoral compartments as detected on magnetic resonance imaging (MRI).

Methods—The Multicenter Osteoarthritis Study is an observational study of individuals with or at risk for knee osteoarthritis (OA). Subjects whose baseline and 30-month follow-up MRIs were read for findings of OA were included. MRI was performed with a 1.0T extremity system. Tibiofemoral compartments were divided into 10 subregions. Cartilage morphology was scored from 0 to 6 and BMLs were scored from 0 to 3. Prevalent cartilage damage and cartilage loss over

Corresponding author: Michel D. Crema, MD, Department of Radiology, Quantitative Imaging Center, Boston University School of Medicine, 820 Harrison Avenue, FGH Building, 3rd Floor, Boston, MA 02118, USA. Tel: +1-617-414-3893; Fax: +1-617-638-6616; michelcrema@gmail.com.

AUTHORS CONTRIBUTIONS Conception and design: all authors; Analysis and interpretation of the data: MDC, DTF, FWR, KW, MDM, JAL, AG; Drafting of the article: all authors; Critical revision of the article for important intellectual content: all authors; Final approval of the article: all authors; Provision of study materials or patients: DTF, MCN, JT, CEL; Statistical expertise: DTF, KW, JAL, MCN; Obtaining of funding: DTF, MCN, JT, CEL.

CONFLICT OF INTERST Michel D. Crema, Frank W. Roemer, and Monica D. Marra are stockholders of Boston Imaging Core Lab (BICL), LLC. Ali Guermazi is president of BICL, LLC. He is also a consultant for MerckSerono, Genzyme, Novartis, Stryker, and AstraZeneca.

time were considered predictors of incident BMLs. Associations were assessed using logistic regression, with adjustments for potential confounders.

Results—Medially, incident BMLs were associated with baseline cartilage damage (adjusted odds ratio (OR) 3.9 [95% CI 3.0, 5.1]), incident cartilage loss (7.3 [95% CI 5.0, 10.7]) and progression of cartilage loss (7.6 [95% CI 5.1, 11.3]) Laterally, incident BMLs were associated with baseline cartilage damage (4.1 [95% CI 2.6, 6.3]), incident cartilage loss (6.0 [95% CI 3.1, 11.8]), and progression of cartilage loss (11.9 [95% CI 6.2, 23.0]).

Conclusion—Prevalent cartilage damage and cartilage loss over time are strongly associated with incident BMLs in the same subregion, supporting the significance of the close interrelation of the osteochondral unit in the progression of knee OA.

Keywords

Bone marrow; cartilage; knee; osteoarthritis; magnetic resonance imaging

INTRODUCTION

The role of subchondral bone marrow edema-like lesions as detected on magnetic resonance imaging in the natural history of knee osteoarthritis has been explored extensively. The presence and behavior of bone marrow edema-like lesions (BMLs) can predict structural progression and pain incidence as well as fluctuation of symptoms in subjects with knee osteoarthritis (OA) [1-12]. These lesions are frequently detected in conjunction with cartilage damage in the same region of the knee [13, 14] and incident BMLs or an increase in BML size over time predict future cartilage loss [3, 5]. Histologically, BMLs represent areas of subchondral bone damage and remodeling, exhibiting features of fibrosis, necrosis, and trabecular abnormalities [15, 16].

Factors leading to increased loading of the subchondral bone such as knee malalignment and meniscal pathology are associated with BMLs in the same tibiofemoral compartment of the knee [1, 5, 17]. BMLs are also associated with concomitant increased local bone density, suggesting that they occur in areas of bone subjected to long-term excess loading [18]. Any increase in focal loading of the bone could increase damage to the bone, especially if the stress exceeds the bone's strain tolerance.

Cartilage has a much lower stiffness that underlying bone and might not reasonably be expected to protect it from direct impulse loads. However, like the meniscus, compressive stresses applied to cartilage are distributed across a broader area than just that impacted cartilage, potentially lessening the impulse to a focal area of underlying bone [19]. This could diminish the bone damage represented by BMLs. If cartilage is damaged, it becomes softer and its collagen network, which helps distribute the load, becomes less competent in serving this protective function.

Thus, OA-related cartilage loss in the tibiofemoral compartments may actually remove tissue that protects the underlying subchondral bone, thereby increasing the focal load transmitted and damaging the bone, resulting in subjacent BMLs.

We attempted to assess specifically the association of MRI-detected prevalent cartilage damage (assessed only at baseline) with incident BMLs in the tibiofemoral compartments of subjects with or at risk for knee OA. Assuming that cartilage loss over time would also contribute to the development of BMLs for the same biomechanical reasons, we also examined the association of cartilage loss over time with incident BMLs.

MATERIALS AND METHODS

Study Design and Subjects

Subjects were participants in the Multicenter Osteoarthritis Study (MOST), a prospective epidemiological study of 3,026 people aged 50 to 79 years with the goal of identifying risk factors for incident and progressive knee OA in a population with or at high risk for OA. They were recruited from two U.S. communities, Birmingham, Alabama and Iowa City, Iowa through mass mailing of letters and study brochures, supplemented by media and community outreach campaigns. The Health Insurance Portability and Accountability Act-compliant study protocol was approved by the Institutional Review Boards at the University of Iowa, University of Alabama at Birmingham, University of California at San Francisco and Boston University School of Medicine. We obtained written informed consent from all patients.

Subjects considered at high risk for knee OA included those who were overweight or obese, those with knee pain, aching or stiffness on most of the last 30 days, a history of knee injury that made it difficult to walk for at least one week, or previous knee surgery. Subjects were excluded if they screened positive for rheumatoid arthritis [20], had ankylosing spondylitis, psoriatic arthritis, reactive arthritis, renal insufficiency that required hemo- or peritoneal dialysis, a history of cancer (except for non-melanoma skin cancer), had or planned to have bilateral knee replacement surgery, were unable to walk without assistance, or were planning to move out of the area in the next three years.

In the present study we included all participants with available baseline and 30-month follow-up MRI readings. These knees were previously selected for reading for one or more of three substudies in MOST: 1) a cohort study of risk factors for radiographic OA progression consisting of randomly selected knees with either patellofemoral or tibiofemoral OA; 2) a case-control study of risk factors for incident radiographic OA; and 3) a case-control study of risk factors for onset of consistent frequent knee pain [2].

Radiographs

At baseline, all subjects underwent weight-bearing postero-anterior fixed flexion knee radiographs using the protocol by Peterfy et al. and a Plexiglas positioning frame (SynaFlexer™) [21]. A musculoskeletal radiologist and a rheumatologist (non-authors), each with over 10 years experience reading study radiographs, independently graded the x-rays according to the Kellgren-Lawrence (KL) scale [22]. Radiographs were presented sequentially with readers blinded to all clinical data and to the MRIs. Radiographic tibiofemoral OA was considered present if the KL grade was 2 or greater. Disagreements on the presence of radiographic OA were adjudicated by a panel of 3 readers (the initial 2 readers and DTF). For knee alignment assessment, long-limb films were acquired with a 14-inch x 51-inch cassette. Mechanical alignment was measured as the angle formed by the intersection of the femoral and tibial mechanical axes. The femoral mechanical axis is the line from the center of the femoral head through the center of the knee, and the tibial mechanical axis is drawn as a line from the center of the ankle to the center of the knee. Neutral alignment was defined as 179-181 degrees, varus malalignment as ≤178 degrees and valgus malalignment as ≥182 degrees.

MRI Acquisition

MRIs were obtained in both knees at baseline and at 30-month follow-up. Images were acquired with a 1.0 T dedicated extremity unit (ONI MSK Extreme 1.0T, GE Healthcare, Wilmington, MA) with a circumferential extremity coil using fat-suppressed (FS) fast spin-echo proton density-weighted (PDw) sequences in two planes, sagittal (TR = 4800 ms, TE =

35 ms, 3 mm slice thickness, 0 mm interslice gap, 32 slices, 288 × 192 matrix, 2 excitations (NEX), 140 × 140 mm field of view (FOV), echo train length (ETL) = 8) and axial (TR = 4680 ms, TE = 13 ms, 3 mm slice thickness, 0 mm interslice gap, 20 slices, 288 × 192 matrix, 2 NEX, 140 × 140 mm FOV, ETL = 8), and a short tau inversion-recovery (STIR) sequence in the coronal plane (TR = 6650 ms, TE = 15 ms, TI = 100 ms, 3 mm slice thickness, 0 mm interslice gap, 28 slices, 256 × 192 matrix, 2 NEX, 140 mm^2 FOV, ETL = 8). Examinations were performed at the University of Alabama at Birmingham and at the University of Iowa at Iowa City with the same MR unit.

MRI Interpretation

MRIs were independently read by two musculoskeletal radiologists (FWR and AG), with 8 and 10 years experience in standardized semiquantitative MRI assessment of knee OA. They were blinded to radiographic OA grade and clinical data, while grading BMLs and cartilage status according to the WORMS system [23]. Scoring with the WORMS system using a 1.0T dedicated extremity MRI system, rather than a 1.5T large-bore MRI, has been shown to provide a moderate to high degree of agreement and accuracy [24]. Baseline and follow-up MRIs were presented paired and in sequence, with the chronological order known to the readers. BMLs and cartilage status were scored in each of the 5 subregions in the medial and lateral tibiofemoral compartments, for a total of 10 subregions per knee.

BML size was scored from 0-3 based on the extent of regional involvement: 0 = none; 1 = <25% of the subregion, 2 = 25-50% of the subregion; 3 = >50% of the subregion. BMLs were defined as poorly-delineated areas of hyperintensity directly adjacent to the subchondral plate on the STIR and PDw FS images [15, 25]. Typical MRI signs of traumatic bone contusions, osteonecrosis, fracture or malignant bone infiltration were grounds for exclusion from the analysis. In fact, only one knee, with a subacute tibial depression fracture at follow-up, was excluded.

Cartilage morphology and signal were scored semiquantitatively from 0 to 6 in each subregion: 0 = normal thickness and signal; 1 = normal thickness but increased signal on PDw or STIR images; 2.0 = partial thickness focal defect <1 cm in greatest width (Figure 2); 2.5 = full thickness focal defect <1 cm in greatest width; 3 = multiple areas of partial-thickness defects intermixed with areas of normal thickness, or a grade 2.0 defect wider than 1 cm but <75% of the region; 4 = diffuse (≥75% of the region) partial-thickness loss; 5 = multiple areas of full thickness loss or a grade 2.5 lesion wider than 1 cm but <75% of the region; 6 = diffuse (≥75% of the region) full-thickness loss. In a modification of WORMS developed specifically for longitudinal readings, a score of 0.5 for cartilage assessment was introduced to reflect subtle within-grade progression that did not fulfill the criteria of a full-grade change. A recent work demonstrated that the within-grade scoring of longitudinal changes in the articular cartilage is clinically relevant since such scoring increases the number of compartments and subregions showing change and is associated with clinically relevant risk factors and outcomes [26]. Any change of ≥0.5 in at least one of 10 tibiofemoral subregions was defined as cartilage loss.

Assessment of meniscal morphology was performed according to WORMS, and the anterior horn, body, and posterior horn of the medial and lateral menisci were graded separately from 0 to 4 (0 = intact; 1 = minor radial tear or parrot-beak tear; 2 = non-displaced tears including horizontal and vertical tears or prior surgical repair; 3 = displaced tears including displaced flap tears and bucket-handle tears, or partial resection or maceration; 4 = complete maceration/destruction or complete resection).

Extrusion of the medial and lateral meniscal body was assessed using coronal STIR images. The reference slice for extrusion assessment in all knees is the one where the medial tibial

spine has the greatest volume [27]. The edge of the tibial plateaus (excluding osteophytes) was used as the reference for measuring extrusion of the body of both menisci (Figure 1). Medial and lateral meniscal extrusion was graded from 0 to 2 (0 = no extrusion; 1 = extrusion ≤ 50% of the body; 2 = extrusion > 50% of the body).

The weighted kappa coefficients of inter-observer reliability (30 knees randomly selected and read by both readers) were 0.66 for the readings of BMLs (comparing 0-3 scores in each subregion) and 0.78 for cartilage morphology (comparing 0-6 scores in each subregion). The weighted kappa coefficients of intra-reader observer reliability (30 knees randomly selected) were 0.8 and 0.94 for the readings of BMLs (comparing 0-3 scores in each subregion), and 0.88 and 0.92 for the readings of cartilage morphology (comparing 0-6 scores in each subregion).

Statistical analysis

Prevalent cartilage damage was defined as grade ≥ 2 detected at baseline. Subregions of knees showing cartilage loss over time were divided into two groups: incident (grades 0 at baseline and ≥ 2 at follow-up) and progression (prevalent cartilage damage with the grade increased by at least 0.5 at follow-up). Incident BMLs (Figure 1) were defined as grade 0 at baseline and ≥ 1 at follow-up. Subregions with prevalent BMLs (grade ≥ 1 at baseline) were excluded. Prevalent cartilage damage was considered a predictor of incident BMLs (outcome); subregions with no prevalent cartilage damage served as the reference group. Cartilage loss over time measured between baseline and 30-month follow-up was also considered a predictor of incident BMLs (outcome) and subregions with no cartilage loss over time served as the reference group. Our units of analysis were the subregions of the tibiofemoral compartments so that we could examine the relationship of cartilage pathology with BMLs.

We assessed the association of prevalent cartilage damage and cartilage loss over time with incident BMLs in the same subregion of both tibiofemoral compartments, using logistic regression with generalized estimated equations to account for correlations among the subregions within a knee (using one knee per person). A subregion with no prevalent BMLs may share a compartment or a knee with other tibiofemoral subregions with prevalent BMLs, and so we performed additional analyses after excluding all knees with any prevalent BML in any tibiofemoral compartments' subregion, and then assessed the same associations as described above.

Adjustment for both analyses included age, gender, body mass index (BMI), knee malalignment, meniscal damage, and meniscal extrusion. All statistical calculations were performed using SAS® software (Version 9.1 for Windows; SAS Institute; Cary, NC).

RESULTS

Participants' characteristics

One thousand three-hundred fifty subjects (1351 knees, 12225 (5890 medial and 6335 lateral) subregions) were included. The mean age of subjects was 62.2 years (±7.9 standard deviation - SD), with a mean (SD; range) BMI of 29.9.0 (±4.8; 18.0-49.0). Further, 61.5% of subjects were women (n=830), and 42.1% had tibiofemoral radiographic OA (KL grade ≥2) at baseline (n=568). Of 21370 subregions analyzed initially, 1252 (5.9%) exhibited BMLs at baseline and were excluded. Many subregions were excluded because they were not assessable, mainly because of motion artifacts or field inhomogeneity at baseline and/or follow-up, which did not allow scoring of the features in these subregions. A total of 9145 (42.8%) subregions were finally excluded. Considering both compartments together, a statistically significant difference was found for age (p=0.01) when considering included

versus excluded subregions, but no difference was found for sex (p=0.67). No significant differences were found for age (p=0.06) and sex (p=0.75) when considering subregions with versus without incident BMLs.

Medial compartment

Incident BMLs, prevalent cartilage damage, and progression of cartilage loss were more frequent at the central subregion of the medial femur; incident cartilage loss was more frequent at the posterior subregion of the medial femur (Table 1). Prevalent cartilage damage showed a significant association with incident BMLs in the same subregion, with an OR of 3.9 (95% confidence intervals 3.0-5.1, p<0.0001), when compared to subregions without prevalent cartilage loss. Compared to subregions with no cartilage loss between baseline and follow-up, both incident cartilage loss and progression of cartilage loss demonstrated a significant association with incident BMLs in the same subregion, with ORs of 7.3 (95% confidence intervals 5.0-10.7, p<0.0001) for incident cartilage loss and 7.6 (95% confidence intervals 5.1-11.3, p<0.0001) for progression of cartilage loss (Table 2).

Lateral compartment

Incident BMLs and progression of cartilage loss were more frequent at the central subregion of the lateral tibia; prevalent cartilage damage and incident cartilage loss were more frequent at the central subregion of the lateral femur (Table 3). Prevalent cartilage loss showed a significant association with incident BMLs in the same subregion, with an OR of 4.1 (95% confidence intervals 2.6-6.3, p<0.0001), when compared to subregions without prevalent cartilage loss. Compared to subregions with no cartilage loss between baseline and follow-up, both incident cartilage loss and progression of cartilage loss demonstrated a significant association with incident BMLs in the same subregion, with ORs of 6.0 (95% confidence intervals 3.1-11.8, p<0.0001) for incident cartilage loss and 11.9 (95% confidence intervals 6.2-23.0, p<0.0001) for progression of cartilage loss (Table 4).

Additional analyses

After 562 knees (4344 subregions) with any prevalent BML in any tibiofemoral subregion were excluded for the additional analysis, 7881 (3939 medial and 3942 lateral) subregions remained. No statistically significant differences were found for age (p=0.1) and sex (p=0.27) when considering knees with any prevalent tibiofemoral BML versus knees with no prevalent tibiofemoral BML. The associations of prevalent cartilage damage with incident BMLs in the same subregion for both compartments remained significant (Tables 5 and 6). The associations of incident cartilage loss and progression of cartilage loss with incident BMLs in the same subregion of both compartments remained significant and stronger than in the previous analyses (Tables 5 and 6).

DISCUSSION

Previous studies have demonstrated that MRI-detected BMLs are predictors of cartilage loss in the tibiofemoral compartments of the knee [3, 5, 10]. In contrast, our results showed that cartilage damage at baseline, as well as cartilage loss over time, is associated with incident BMLs in the same subregion of the tibiofemoral compartments. The reciprocal relationship might be explained by the close interrelation between subchondral bone and articular cartilage in the pathogenesis of knee OA.

BMLs are a highly variable feature in patients with or at risk for knee OA, and their size may increase or decrease over time [2, 3, 5, 28]. Felson et al. [1] demonstrated that BMLs are powerful predictors of radiographic progression of knee OA. Fluctuations in the size of the lesion over time seem to have a direct effect on progression of knee OA. Roemer et al.

[3] showed that subregions within the knee having incident and progressive BMLs demonstrate a higher risk of cartilage loss at follow-up. Hunter et al. [5] demonstrated that, compared to stable BMLs, enlarging lesions are strongly associated with cartilage loss at follow-up. Other recent studies have also demonstrated the predictive effect of BMLs on cartilage loss [11, 12], and such lesions were also shown to predict a worse outcome in subjects with OA at baseline, increasing the risk of total knee arthroplasty compared with subjects without lesions [12]. However, both studies [11, 12] used inappropriate MRI techniques to assess BMLs [29, 30], making the interpretation of their results unclear. It has been hypothesized that cartilage loss is secondary to BMLs, as the integrity of the cartilage may be dependent on the mechanical properties of the underlying subchondral bone. Because of the stiffness and higher local mineral density of areas of subchondral bone with BMLs, the bone may be incapable of dissipating the forces on the joint during loading, thereby transmitting more load onto overlying cartilage, and causing the cartilage to breakdown [31]. Previous experimental studies (animal models) with histological assessment of the subchondral bone and the articular cartilage also support that damage to the subchondral bone may lead to adjacent cartilage damage [32-35].

On the other hand, our results showed that preserved hyaline cartilage lowers the risk of developing BMLs. We suggest that this may relate to the ability of intact cartilage to distribute compressive loads so that the maximal stress from these loads is diminished. When cartilage's collagen network is damaged, its effectiveness in serving this function should decline. In fact, previous studies have shown that factors that lead to increased loading on the tibiofemoral compartments, such as knee malalignment and meniscal pathology, are related to BMLs [1, 5, 18]. We controlled for these factors in our analysis, so that we could focus on cartilage integrity as a protective risk factor.

Mechanical limb alignment is thought to directly affect location, prevalence, and change in BMLs, as medial knee lesions occur mainly in individuals with varus-aligned limbs, and lateral lesions occur mostly in those with valgus-aligned limbs [1, 5]. One could argue that the increased load on the tibiofemoral compartments due to malalignment could be directly responsible for adjacent cartilage loss, and BMLs would play a secondary role, as such lesions are highly associated with knee malalignment. This is supported by previous work from Felson et al., in which the predictive effect of BMLs on cartilage loss was evident only when there was no adjustment for knee malalignment: making the adjustment greatly diluted the effect [1].

Pathology involving the menisci, which are responsible for load-bearing and shock absorption in the tibiofemoral compartments [36, 37], has been shown to be related to concomitant BMLs. Meniscal pathology is highly associated with and predicts lesions in the same tibiofemoral compartments [18, 38]. Thus, loss of meniscal function may increase loading to the underlying subchondral bone, leading to BMLs.

In the present study, we hypothesized that subregions in the tibiofemoral compartments with cartilage damage might develop BMLs longitudinally, as the diminished integrity of the cartilage could alter its biomechanical properties and thus its response to loading, which in turn could increase loading on the adjacent subchondral bone. The results from our study support such a hypothesis, with the association of both cartilage damage and cartilage loss over time with incident BMLs demonstrated in both tibiofemoral compartments. In contrast to the previously demonstrated effect of BMLs on cartilage loss, which may be influenced by knee malalignment, the association of cartilage damage and cartilage loss over time with incident BMLs in the tibiofemoral compartments is independent of knee malalignment, as well as of other factors that can increase loading to the tibiofemoral subchondral bone, such

as meniscal tears and meniscal extrusion. One previous study demonstrated that cartilage defects predicted an increase in BMLs over time in the tibiofemoral compartments [39].

In the subregional approach used initially for testing the associations, one could argue that excluding only subregions with prevalent BMLs may have introduced bias, since other subregions in the same compartment or in the contralateral compartment could have prevalent BMLs. It is not known if the risk of incident BMLs is higher in subregions of knees with baseline BMLs in other tibiofemoral subregions. For that reason, we performed additional analyses after excluding all knees with any prevalent BML in any tibiofemoral subregion, and we found that the associations with incident BMLs remained significant for prevalent cartilage damage, and were significant and even stronger for incident cartilage loss and progression of cartilage loss.

In the present study, we only considered MRI-detected edema like BMLs since only such pattern of subchondral BMLs demonstrated strong evidence to be clinically relevant regarding progression of knee OA and knee symptoms, independently of the presence of other MRI features [1-12]. Other possible patterns of degenerative changes in the subchondral bone detected on MRI such as sclerosis and cysts did not demonstrate to be clinically relevant independently of other features [40,41].

There are some limitations to this study. First, the MRIs were presented sequentially, and readers were aware of the chronological order of images. This could, perhaps, bias the readers to expect more change. On the other hand, it has been found that when readers are blinded to chronological order, sensitivity to clinically relevant changes actually decreases, compared to unblinded assessment [42-44]. Further, previous analysis in this study sample showed comparable weighted kappa coefficients when assessing a subset of randomly selected knees blinded to time point [4]. Second and unfortunately, MRI does not allow for separate assessment of two adjacent structures such as subchondral bone and articular cartilage, as both are visualized within the same image and specific features (such as cartilage damage and BMLs) cannot be separately blinded. Third, one could argue that the image quality of 1.0T MRI is inferior to 1.5T systems. However, WORMS scoring using a 1.0T dedicated extremity MRI is possible with a moderate to high degree of agreement and accuracy compared with WORMS assessment of 1.5T large-bore MRI [24]. Fourth, even though we could prove a strong association of cartilage damage and cartilage loss over time with incident BMLs, we cannot be sure about the chronological order of these structural changes (e.g. cartilage loss precedes BMLs) as we assessed only two distinct time points. This is true especially for BMLs, which vary widely over time [2, 3, 5, 28]. Only repeated examinations with at least 3 points of observation at shorter intervals could demonstrate the chronological order of these features. Finally, there are radiological differential diagnoses for degenerative BMLs, the most common being traumatic bone contusions [45, 46]. We carefully excluded knees with an unequivocal radiologic differential diagnosis prior to analysis.

In summary, we demonstrated that prevalent cartilage damage and cartilage loss over time are strongly associated with incident BMLs in the same subregion of the tibiofemoral compartments. We adjusted our results for known mechanical factors that can increase loading to the tibiofemoral compartments such as knee malalignment, meniscal damage, and meniscal extrusion, which suggests that cartilage damage and cartilage loss may be independent predictors of incident BMLs. In light of previous work, our findings support the concept of the “osteochondral unit” and the close interrelation of cartilage and subchondral bone. Once damage to the articular cartilage surface or the subchondral bone is apparent the risk of structural deterioration in the adjacent tissue seems to be markedly increased.

Acknowledgments

We would like to thank all staff at the Coordinating Center at the University of California at San Francisco. We would also like to thank all staff at the clinical sites in Iowa and Alabama. Finally, we would like to express our thanks to all participants of the MOST study.

FUNDING SOURCE Supported by NIH grants from the National Institute of Aging to Drs. Lewis (U01-AG-18947), Torner (U01-AG-18832), Nevitt (U01-AG-19069), and Felson (U01-AG-18820) and NIH AR47785.

REFERENCES

1. Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med. 2003; 139:330–6. [PubMed: 12965941]
2. 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]
3. Roemer FW, Guermazi A, Javaid MK, Lynch JA, Niu J, Zhang Y, et al. Change in MRI-detected subchondral bone marrow lesions is associated with cartilage loss: the MOST Study. A longitudinal multicentre study of knee osteoarthritis. Ann Rheum Dis. 2009; 68:1461–5. [PubMed: 18829615]
4. Crema MD, Roemer FW, Zhu Y, Marra MD, Niu J, Zhang Y, et al. Subchondral cystlike lesions develop longitudinally in areas of bone marrow edema-like lesions in Patients with or at risk for knee osteoarthritis: detection with MR imaging--the MOST study. Radiology. 2010; 256:855–62. [PubMed: 20530753]
5. Hunter DJ, Zhang Y, Niu J, Goggins J, Amin S, LaValley MP, et al. Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. Arthritis Rheum. 2006; 54:1529–35. [PubMed: 16646037]
6. Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM, et al. The association of bone marrow lesions with pain in knee osteoarthritis. Ann Intern Med. 2001; 134:541–9. [PubMed: 11281736]
7. Roemer FW, Neogi T, Nevitt MC, Felson DT, Zhu Y, Zhang Y, et al. Subchondral bone marrow lesions are highly associated with, and predict subchondral bone attrition longitudinally: the MOST study. Osteoarthritis Cartilage. 2010; 18:47–53. [PubMed: 19769930]
8. Zhang Y, Nevitt MC, Niu J, Lewis C, Torner J, Guermazi A, et al. Fluctuation of knee pain and changes in bone marrow lesions, effusions and synovitis on magnetic resonance imaging. Arthritis Rheum. 2011; 63:691–9. [PubMed: 21360498]
9. Scher C, Craig J, Nelson F. Bone marrow edema in the knee in osteoarthrosis and association with total knee arthroplasty within a three-year follow-up. Skeletal Radiol. 2008; 37:609–17. [PubMed: 18463865]
10. Kothari A, Guermazi A, Chmiel JS, Dunlop D, Song J, Almagor O, et al. Within-subregion relationship between bone marrow lesions and subsequent cartilage loss in knee osteoarthritis. Arthritis Care Res (Hoboken). 2010; 62:198–203. [PubMed: 20191518]
11. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Abram F, Choquette D, Haraoui B, et al. Correlation between bone lesion changes and cartilage volume loss in patients with osteoarthritis of the knee as assessed by quantitative magnetic resonance imaging over a 24-month period. Ann Rheum Dis. 2008; 67:683–8. [PubMed: 17728333]
12. Tanamas SK, Wluka AE, Pelletier JP, Pelletier JM, Abram F, Berry PA, et al. Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study. Rheumatology (Oxford). 2010; 49:2413–9. [PubMed: 20823092]
13. Guymer E, Baranyay F, Wluka AE, Hanna F, Bell RJ, Davis SR, et al. A study of the prevalence and associations of subchondral bone marrow lesions in the knees of healthy, middle-aged women. Osteoarthritis Cartilage. 2007; 15:1437–42. [PubMed: 17560134]
14. Baranyay FJ, Wang Y, Wluka AE, English DR, Giles GG, Sullivan RO, et al. Association of bone marrow lesions with knee structures and risk factors for bone marrow lesions in the knees of

clinically healthy, community-based adults. Semin Arthritis Rheum. 2007; 37:112–8. [PubMed: 17391738]

15. Zanetti M, Bruder E, Romero J, Hodler J. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. Radiology. 2000; 215:835–40. [PubMed: 10831707]
16. Taljanovic MS, Graham AR, Benjamin JB, Gmitro AF, Krupinski EA, Schwartz SA, et al. Bone marrow edema pattern in advanced hip osteoarthritis: quantitative assessment with magnetic resonance imaging and correlation with clinical examination, radiographic findings, and histopathology. Skeletal Radiol. 2008; 37:423–31. [PubMed: 18274742]
17. Lo GH, Hunter DJ, Nevitt MC, Lynch J, McAlindon TE, OAI Investigators Group. Strong association of MRI meniscal derangement and bone marrow lesions in knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthritis Cartilage. 2009; 17:743–7. [PubMed: 19097919]
18. Lo GH, Hunter DJ, Zhang Y, McLennan CE, Lavalley MP, Kiel DP, et al. Bone marrow lesions in the knee are associated with increased local bone density. Arthritis Rheum. 2005; 52:2814–21. [PubMed: 16145676]
19. Mow, VC.; Hung, CT. Mechanical properties of normal and osteoarthritic articular cartilage, and the mechanobiology of chondrocytes. In: Brandt, KD.; Doherty, M.; Lohmander, LS., editors. Osteoarthritis. Pathogenesis of osteoarthritis. 2nd edition. Oxford University Press; NY, NY: 2003. p. 102-112.Chapter 7
20. Karlson EW, Sanchez-Guerrero J, Wright EA, Lew RA, Daltroy LH, Katz JN, et al. A connective tissue disease screening questionnaire for population studies. Ann Epidemiol. 1995; 5:297–302. [PubMed: 8520712]
21. Peterfy C, Lynch JA, Miaux Y, et al. Non-fluoroscopic method for flexed radiography of the knee that allows reproducible joint-space width measurement [abstr]. Arthritis Rheum. 1998; 41(suppl):S361.
22. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957; 16:494–502. [PubMed: 13498604]
23. Peterfy C, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage. 2004; 12:177–90. [PubMed: 14972335]
24. Roemer FW, Lynch JA, Niu J, Zhang Y, Crema MD, Tolstykh I, et al. A comparison of dedicated 1.0 T extremity MRI vs large-bore 1.5 T MRI for semiquantitative whole organ assessment of osteoarthritis: the MOST study. Osteoarthritis Cartilage. 2010; 18:168–74. [PubMed: 19766580]
25. Bergman AG, Willén HK, Lindstrand AL, Pettersson HT. Osteoarthritis of the knee: correlation of subchondral MR signal abnormalities with histopathologic and radiographic features. Skeletal Radiol. 1994; 23:445–8. [PubMed: 7992110]
26. Roemer FW, Nevitt MC, Felson DT, Niu J, Lynch JA, Crema MD, et al. MRI-based semiquantitative cartilage morphology and bone marrow lesions assessment: validity of within-grade scoring of longitudinal changes in the MOST cohort. Osteoarthritis Cartilage. 2011; 19(suppl 1):S165–6.
27. Crema MD, Roemer FW, Felson DT, Englund M, Wang K, Jarraya M, et al. Factors associated with meniscal extrusion in knees with or at risk for knee osteoarthritis: the Multicenter Osteoarthritis Study. Radiology. 2012; 264:494–503. [PubMed: 22653191]
28. 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. [PubMed: 17823802]
29. Roemer FW, Hunter DJ, Guermazi A. MRI-based semiquantitative assessment of subchondral bone marrow lesions in osteoarthritis research. Osteoarthritis Cartilage. 2009; 17:414–5. author reply 416-7. [PubMed: 18948039]
30. Peterfy CG, Gold GE, Eckstein F, Cicuttini F, Dardzinski B, Stevens R. MRI protocols for whole-organ assessment of the knee in osteoarthritis. Osteoarthritis Cartilage. 2006; 14(Suppl A):A95–111. [PubMed: 16750915]
31. Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. Clin Orthop Relat Res. 1986; 213:34–40. [PubMed: 3780104]

32. Lacourt M, Gao C, Li A, Girard C, Beauchamp G, Henderson JE, et al. Relationship between cartilage and subchondral bone lesions in repetitive impact trauma-induced equine osteoarthritis. Osteoarthritis Cartilage. 2012; 20:572–83. [PubMed: 22343573]
33. Thomsen JS, Straarup TS, Danielsen CC, Oxlund H, Brüel A. Relationship between articular cartilage damage and subchondral bone properties and meniscal ossification in the Dunkin Hartley guinea pig model of osteoarthritis. Scand J Rheumatol. 2011; 40:391–9. [PubMed: 21679094]
34. Botter SM, van Osch GJ, Waarsing JH, van der Linden JC, Vehaar JA, Pols HA, et al. Cartilage damage pattern in relation to subchondral plate thickness in a collagenase-induced model of osteoarthritis. Osteoarthritis Cartilage. 2008; 16:506–14. [PubMed: 17900935]
35. Lahm A, Kreuz PC, Oberst M, Haberstroh J, Uhl M, Maier D. Subchondral and trabecular bone remodeling in canine experimental osteoarthritis. Arch Orthop Trauma Surg. 2006; 126:582–7. [PubMed: 16331520]
36. Seedhom BB, Dowson D, Wright V. Proceedings: Functions of the menisci. A preliminary study. Ann Rheum Dis. 1974; 33:111. [PubMed: 4821376]
37. Walker PS, Erkman MJ. The role of the menisci in force transmission across the knee. Clin Orthop Relat Res. 1975; 109:184–92. [PubMed: 1173360]
38. Englund M, Guermazi A, Roemer FW, Yang M, Zhang Y, Nevitt MC, et al. Meniscal pathology on MRI increases the risk for both incident and enlarging subchondral bone marrow lesions of the knee: the MOST Study. Ann Rheum Dis. 2010; 69:1796–802. [PubMed: 20421344]
39. Dore D, Martens A, Quinn S, Ding C, Winzenberg T, Zhai G, et al. Bone marrow lesions predict site-specific cartilage defect development and volume loss: a prospective study in older adults. Arthritis Res Ther. 2012; 12:R222. [PubMed: 21190554]
40. Crema MD, Cibere J, Sayre EC, Roemer FW, Wong H, Thorne A, et al. The association of MRI-detected subchondral bone marrow sclerosis with cartilage loss in a cohort of subjects with knee pain. Osteoarthritis Cartilage. 2012; 20(Suppl 1):S207–8.
41. Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualized on MRI explain knee pain in knee osteoarthritis? a systematic review. Ann Rheum Dis. 2011; 70:60–7. [PubMed: 20829200]
42. Bruynesteyn K, Van Der Heijde D, Boers M, Saudan A, Peloso P, Paulus H, et al. Detecting radiological changes in rheumatoid arthritis that are considered important by clinical experts: influence of reading with or without known sequence. J Rheumatol. 2002; 29:2306–12. [PubMed: 12415585]
43. Ross PD, Huang C, Karpf D, Lydick E, Coel M, Hirsch L, et al. Blinded reading of radiographs increases the frequency of errors in vertebral fracture detection. J Bone Miner Res. 1996; 11:1793–800. [PubMed: 8915788]
44. Gensburger D, Roux JP, Arlot M, Sornay-Rendu E, Ravaud P, Chapurlat R. Influence of blinding sequence of radiographs on the reproducibility and sensitivity to change of joint space width measurement in knee osteoarthritis. Arthritis Care Res (Hoboken). 2010; 62:1699–705. [PubMed: 20665746]
45. Boks SS, Vroegindeweij D, Koes BW, Hunink MG, Bierma-Zeinstra SM. Follow-up of occult bone lesions detected at MR imaging: systematic review. Radiology. 2006; 238:853–62. [PubMed: 16452394]
46. Roemer FW, Frobell R, Hunter DJ, Crema MD, Fischer W, Bohndorf K, et al. MRI-detected subchondral bone marrow signal alterations of the knee joint: terminology, imaging appearance, relevance and radiological differential diagnosis. Osteoarthritis Cartilage. 2009; 17:1115–31. [PubMed: 19358902]

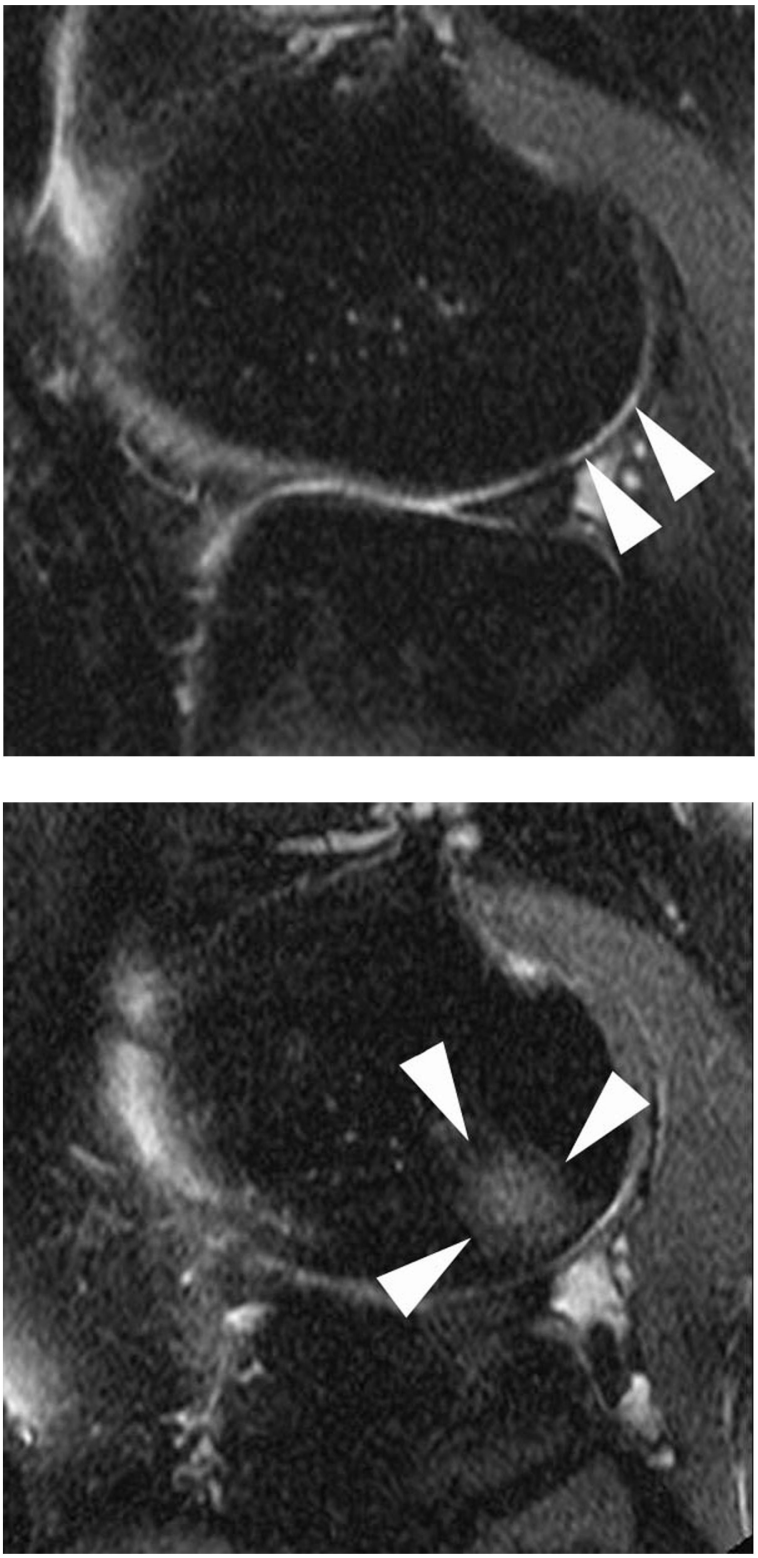

Figure 1.
Incident BML. A) Sagittal fat-suppressed proton density-weighted MRI acquired at baseline shows cartilage thinning at the posterior subregion of the lateral femoral condyle

(arrowheads). The adjacent subchondral bone is normal. Note also cartilage thinning in the central subregion of the lateral femoral condyle. B) Sagittal fat-suppressed proton density-weighted MRI of the same region of the knee acquired at 30-month follow-up demonstrates an incident BML in the same subregion (arrowheads).

Table 1

Distribution of MRI features assessed in medial tibiofemoral compartment's subregions. CF = central subregion of medial femur; PF = posterior subregion of medial femur; AT = anterior subregion of medial tibia; CT = central subregion of medial tibia; PT posterior subregion of medial tibia.

	Subregions*					Total
	CF	PF	AT	CT	PT	
Incident BMLs	92 (28.9%)	63 (19.8%)	48 (15.1%)	83 (26.1%)	32 (10.1%)	318
Prevalent cartilage damage	577 (33.9%)	308 (18.1%)	141 (8.3%)	469 (27.5 %)	207 (12.2%)	1702
Incident cartilage loss	48 (21.8%)	59 (26.8%)	31 (14.1%)	41 (18.6%)	41 (18.6%)	220
Progression of cartilage loss	81 (41.5%)	31 (15.9%)	11 (5.6%)	52 (26.7%)	20 (10.3%)	195

*Features could occur in multiple subregions in the same knee.

Table 2

Associations assessed at the medial tibiofemoral compartment.

	Incident BMLs (30-month) in subregions		Adjusted OR* (95% confidence intervals)
	Absence (score = 0)	Presence (score ≥ 1)	
Normal cartilage morphology at baseline	4072 (69.1%)	116 (2.0%)	**1.0 (reference)**
Prevalent cartilage damage	1500 (25.5%)	202 (3.4%)	3.9 (3.0, 5.1)**
No cartilage loss between BL and 30-month FU	5271 (89.5%)	204 (3.5%)	**1.0 (reference)**
Incident cartilage loss	164 (2.8%)	56(1.0%)	7.3 (5.0, 10.7)**
Progression of cartilage loss	137 (2.3%)	58 (1%)	7.6 (5.1, 11.3)**

*Adjusted for age, gender, BMI, varus knee malalignment, medial meniscal damage, and medial meniscal extrusion.

**Statistically significant defined as $p<0.05$.

Table 3

Distribution of MRI features assessed in lateral tibiofemoral compartment's subregions. CF = central subregion of lateral femur; PF = posterior subregion of lateral femur; AT = anterior subregion of lateral tibia; CT = central subregion of lateral tibia; PT posterior subregion of lateral tibia.

	Subregions*					Total
	CF	PF	AT	CT	PT	
Incident BMLs	22 (18.2%)	31 (25.6%)	14 (11.6%)	35 (28.9%)	19 (15.7%)	121
Prevalent cartilage damage	383 (35.5%)	111 (10.3%)	45 (4.2%)	273 (25.3 %)	268 (24.8%)	1080
Incident cartilage loss	43 (32.1%)	23 (17.2%)	8 (6.0%)	34 (25.4%)	26 (19.4%)	134
Progression of cartilage loss	30 (27.3%)	19 (17.3%)	2 (1.8%)	36 (32.7%)	23 (20.9%)	110

*Features could occur in multiple subregions in the same knee.

Osteoarthritis Cartilage. Author manuscript; available in PMC 2014 February 01.

Table 4

Associations assessed at the lateral tibiofemoral compartment.

	Incident BMLs (30-month) in subregions		Adjusted OR* (95% confidence intervals)
	Absence (score = 0)	Presence (score ≥ 1)	
Normal cartilage morphology at baseline	5199 (82.1%)	56 (0.9%)	**1.0 (reference)**
Prevalent cartilage damage	1015 (16.0%)	65 (1.0%)	4.1 (2.6, 6.3)**
No cartilage loss between BL and 30-month FU	6011 (94.9%)	80 (1.3%)	**1.0 (reference)**
Incident cartilage loss	118 (1.9%)	16(0.3%)	6.0 (3.1, 11.8)**
Progression of cartilage loss between	85 (1.3%)	25 (0.4%)	11.9 (6.2, 23.0)**

*Adjusted for age, gender, BMI, valgus knee malalignment, lateral meniscal damage, and lateral meniscal extrusion.

**Statistically significant defined as $p<0.05$.

Table 5

Associations assessed at the medial tibiofemoral compartment after excluding all knees with any prevalent tibiofemoral BML.

	Incident BMLs (30-month) in subregions		Adjusted OR* (95% confidence intervals)
	Absence (score = 0)	Presence (score ≥ 1)	
Normal cartilage morphology at baseline	3050 (77.4%)	76 (1.9%)	**1.0 (reference)**
Prevalent cartilage damage	746 (19.0%)	67 (1.7%)	2.6 (1.8, 3.9) **
No cartilage loss between BL and 30-month FU	3613 (91.7%)	78 (2.0%)	**1.0 (reference)**
Incident cartilage loss	110 (2.8%)	39 (1.0%)	12.5 (7.7, 20.1) **
Progression of cartilage loss	73 (1.9%)	26 (0.6%)	11.5 (6.1, 21.4) **

* Adjusted for age, gender, BMI, varus knee malalignment, medial meniscal damage, and medial meniscal extrusion.

** Statistically significant defined as $p<0.05$.

Table 6

Associations assessed at the lateral tibiofemoral compartment after excluding all knees with any prevalent tibiofemoral BML.

	Incident BMLs (30-month) in subregions		Adjusted OR* (95% confidence intervals)
	Absence (score = 0)	Presence (score ≥ 1)	
Normal cartilage morphology at baseline	3391 (86.0%)	35 (0.9%)	**1.0 (reference)**
Prevalent cartilage damage	488 (12.4%)	28 (0.7%)	4.4 (2.3, 8.3)**
No cartilage loss between BL and 30-month FU	3769 (95.6%)	38 (1.0%)	**1.0 (reference)**
Incident cartilage loss	68 (1.7%)	11 (0.3%)	12.8 (5.7, 28.8)**
Progression of cartilage loss between	42 (1.1%)	14 (0.3%)	22.3 (9.2, 54.1)**

*Adjusted for age, gender, BMI, valgus knee malalignment, lateral meniscal damage, and lateral meniscal extrusion.

**Statistically significant defined as $p<0.05$.